Additional File 1

An epithelial-to-mesenchymal transition model recovers and predicts critical mutations underlying hepatic cancer stem cells emergence

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Experimental evidence supporting the new regulatory interactions included in the hEMT model

Source	Target	Edge	Regulation type	Description	References
c-Myc	BMI1	(+)	Transcriptional	c-Myc is recruited to the *BMI1* promoter. c-Myc activates BMI1 expression.	Guney, I., Wu, S., & Sedivy, J. M. (2006). Reduced c-Myc signaling triggers telomere-independent senescence by regulating Bmi-1 and p16INK4a. Proceedings of the National Academy of Sciences of the United States of America, 103(10), 3645–3650. https://doi.org/10.1073/pnas.0600069103 Wang, H. B., Liu, G. H., Zhang, H., Xing, S., Hu, L. J., Zhao, W. F., … Zeng, M. S. (2013). Sp1 and c-Myc regulate transcription of BMI1 in nasopharyngeal carcinoma. FEBS Journal, 280(12), 2929–2944. https://doi.org/10.1111/febs.12299
SOX9	BMI1	(+)	Transcriptional	Sox9 is recruited to the *Bmi1* promoter. SOX9 activates BMI1 expression.	Matheu, A., Collado, M., Wise, C., Manterola, L., Cekaite, L., Tye, A. J., … Lovell-Badge, R. (2012). Oncogenicity of the developmental transcription factor Sox9. Cancer Research, 72(5), 1301–1315. https://doi.org/10.1158/0008-5472.CAN-11-3660
E2F1	BMI1	(+)	Transcriptional	E2F1 is recruited to the *BMI1* promoter. E2F1 activates BMI1 expression.	Nowak, K., Kerl, K., Fehr, D., Kramps, C., Gessner, C., Killmer, K., … Lutz, W. (2006). BMI1 is a target gene of E2F-1 and is strongly expressed in primary neuroblastomas. Nucleic Acids Research, 34(6), 1745–1754. https://doi.org/10.1093/nar/gkl119
miR-200c	BMI1	(-)	Post-transcriptional	BMI1 is a target of miR-200c.	Wellner, U., Schubert, J., Burk, U. C., Schmalhofer, O., Zhu, F., Sonntag, A., Waldvogel, B., Vannier, C., Darling, D., Hausen, A., Brunton, V. G., Morton, J., Sansom, O., Schüler, J., Stemmler, M. P., Herzberger, C., Hopt, U., & Keck, T. (2009). The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. Nature Cell Biology, 11(12). https://doi.org/10.1038/ncb1998 Qiu, M., Liang, Z., Chen, L., Tan, G., Liu, L. E. I., Wang, K., Chen, H., & Liu, J. (2017). MicroRNA - 200c suppresses cell growth and metastasis by targeting Bmi - 1 and E2F3 in renal cancer cells. 1329–1336. https://doi.org/10.3892/etm.2017.4147
NANOG	BMI1	(+)	Transcriptional	NANOG is recruited to the *BMI1* promoter. NANOG activates *BMI1* promoter.	Xie, X., Piao, L., Cavey, G. S., Old, M., Teknos, T. N., Mapp, A. K., & Pan, Q. (2013). Phosphorylation of Nanog is essential to regulate Bmi1 and promote tumorigenesis. (May 2012), 1–13. https://doi.org/10.1038/onc.2013.173
p21	CDK6	(+)	Prot-prot Interaction	CDK6 is inhibited by p21.	Harper, J. W., Elledge, S. J., Keyomarsi, K., Dynlacht, B., Tsai, L. H., Zhang, P., Dobrowolski, S., Bai, C., Connell-Crowley, L., Swindell, E., Fox, M. P., & Wei, N. (1995). Inhibition of cyclin-dependent kinases by p21. Molecular Biology of the Cell, 6(4), 387–400. https://doi.org/10.1091/mbc.6.4.387

TGF-β1	c-Myc	(-)	Transcriptional	TGF-β1 signaling represses the *c-Myc* promoter.	Frederick, J. P., Liberati, N. T., Waddell, D. S., Shi, Y., & Wang, X.-F. (2004). Transforming Growth Factor β-Mediated Transcriptional Repression of c-myc Is Dependent on Direct Binding of Smad3 to a Novel Repressive Smad Binding Element. Molecular and Cellular Biology, 24(6), 2546–2559. https://doi.org/10.1128/mcb.24.6.2546-2559.2004 Yagi, K., Furuhashi, M., Aoki, H., Goto, D., Kuwano, H., Sugamura, K., … Kato, M. (2002). c-myc is a downstream target of the Smad pathway. Journal of Biological Chemistry, 277(1), 854–861. https://doi.org/10.1074/jbc.M104170200
β-catenin	c-Myc	(+)	Transcriptional	*c-Myc* promoter is activated by β-catenin signaling.	He, T. C., Sparks, A. B., Rago, C., Hermeking, H., Zawel, L., Da Costa, L. T., … Kinzler, K. W. (1998). Identification of c-MYC as a target of the APC pathway. Science, 281(5382), 1509–1512. https://doi.org/10.1126/science.281.5382.1509
p53	c-Myc	(-)	Transcriptional	p53 was recruited to the *c-Myc* promoter. p53 represses the c-Myc expression	Ho, J. S. L., Ma, W., Mao, D. Y. L., & Benchimol, S. (2005). p53-Dependent Transcriptional Repression of c-myc Is Required for G1 Cell Cycle Arrest. Molecular and Cellular Biology, 25(17), 7423–7431. https://doi.org/10.1128/mcb.25.17.7423-7431.2005
SOX2	c-Myc	(+)	Transcriptional	Sox2 is recruited to the *c-Myc* promoter. SOX2 activates c-Myc expression.	Kwan, K. Y., Shen, J., & Corey, D. P. (2015). C-MYC transcriptionally amplifies SOX2 target genes to regulate self-renewal in multipotent otic progenitor cells. Stem Cell Reports, 4(1), 47–60. https://doi.org/10.1016/j.stemcr.2014.11.001 Chen, S., Xu, Y., Chen, Y., Li, X., Mou, W., Wang, L., … Li, N. (2012). SOX2 gene regulates the transcriptional network of oncogenes and affects tumorigenesis of human lung cancer cells. PloS One, 7(5), 1–12. https://doi.org/10.1371/journal.pone.0036326
NF-κB	c-Myc	(+)	Transcriptional	NF-κB increases the *c-Myc* promoter activity.	La Rosa, F. A., Pierce, J. W., & Sonenshein, G. E. (1994). Differential regulation of the c-myc oncogene promoter by the NF-kappa B rel family of transcription factors. Molecular and Cellular Biology, 14(2), 1039–1044. https://doi.org/10.1128/mcb.14.2.1039 Kim, D. W., Gazourian, L., Quadri, S. A., Raphaëlle, Sherr, D. H., & Sonenshein, G. E. (2000). The RelA NF-κB subunit and the aryl hydrocarbon receptor (AhR) cooperate to transactivate the c-myc promoter in mammary cells. Oncogene, 19(48), 5498–5506. https://doi.org/10.1038/sj.onc.1203945
HNF4A	c-Myc	(-)	Transcriptional	HNF4A is recruited to the *c-Myc* promoter. HNF4A represses c-Myc expression.	Qinyu, L., Long, C., Zhen-dong, D., Min-min, S., Wei-ze, W., & Wei-ping, Y. (2013). FOXO6 promotes gastric cancer cell tumorigenicity via upregulation of C-myc. FEBS Letters, 587(14), 2105–2111. https://doi.org/10.1016/j.febslet.2013.05.027 Walesky, C., Edwards, G., Borude, P., Gunewardena, S., O'Neil, M., Yoo, B., & Apte, U. (2013). Hepatocyte nuclear factor 4 alpha deletion promotes diethylnitrosamine-

					induced hepatocellular carcinoma in rodents. Hepatology (Baltimore, Md.), 57(6), 2480–2490. https://doi.org/10.1002/hep.26251
YAP1	c-Myc	(+)	Transcriptional	YAP1 is recruited to the *c-Myc* promoter. YAP knockdown decreases c-Myc expression.	Schütte, U., Bisht, S., Heukamp, L. C., Kebschull, M., Florin, A., Haarmann, J., … Feldmann, G. (2014). Hippo signaling mediates proliferation, invasiveness, and metastatic potential of clear cell renal cell carcinoma. Translational Oncology, 7(2), 309–321. https://doi.org/10.1016/j.tranon.2014.02.005
miR-34a	c-Myc	(-)	Post-transcriptional	c-Myc is a target of miR-34a.	Yamamura, S., Saini, S., Majid, S., Hirata, H., Ueno, K., Chang, I., Tanaka, Y., Gupta, A., & Dahiya, R. (2012). MicroRNA-34a suppresses malignant transformation by targeting c-Myc transcriptional complexes in human renal cell carcinoma. Carcinogenesis, 33(2), 294–300. https://doi.org/10.1093/carcin/bgr286
p16	Cyclin D1	(-)	Transcriptional	p16 decreases the *CCND1* promoter activity.	D'Amico, M., Wu, K., Fu, M., Rao, M., Albanese, C., Russell, R. G., … Pestell, R. G. (2004). The inhibitor of cyclin-dependent kinase 4a/alternative reading frame (INK4a/ARF) locus encoded proteins p16INK4a and p19ARF repress cyclin D1 transcription through distinct cis elements. Cancer Research, 64(12), 4122–4130. https://doi.org/10.1158/0008-5472.CAN-03-2519
SOX2	Cyclin D1	(-)	Transcriptional	Cyclin D1 is directly regulated at the transcriptional level and indirectly through MiR-302 regulation by SOX2.	Hagey, D. W., & Muhr, J. (2014). Sox2 Acts in a Dose-Dependent Fashion to Regulate Proliferation of Cortical Progenitors. Cell Reports, 9(5), 1908–1920. https://doi.org/10.1016/j.celrep.2014.11.013 Greer Card, D. A., Hebbar, P. B., Li, L., Trotter, K. W., Komatsu, Y., Mishina, Y., & Archer, T. K. (2008). Oct4/Sox2-Regulated miR-302 Targets Cyclin D1 in Human Embryonic Stem Cells. Molecular and Cellular Biology, 28(20), 6426–6438. https://doi.org/10.1128/mcb.00359-08
NF-κB	Cyclin D1	(+)	Transcriptional	NF-κB activates the *CCND1* promoter.	Joyce, D., Bouzahzah, B., Fu, M., Albanese, C., D'Amico, M., Steer, J., … Pestell, R. G. (1999). Integration of Rac-dependent regulation of cyclin D1 transcription through a nuclear factor-κB-dependent pathway. Journal of Biological Chemistry, 274(36), 25245–25249. https://doi.org/10.1074/jbc.274.36.25245 Guttridge, D. C., Albanese, C., Reuther, J. Y., Pestell, R. G., & Baldwin, A. S. (1999). NF-κB Controls Cell Growth and Differentiation through Transcriptional Regulation of Cyclin D1. Molecular and Cellular Biology, 19(8), 5785–5799. https://doi.org/10.1128/mcb.19.8.5785
YAP1	Cyclin D1	(+)	Transcriptional	*CCND1* promoter is activated by YAP/TEAD signaling.	Mizuno, T., Murakami, H., Fujii, M., Ishiguro, F., Tanaka, I., Kondo, Y., … Sekido, Y. (2012). YAP induces malignant mesothelioma cell proliferation by upregulating transcription of cell cycle-promoting genes. Oncogene, 31(49), 5117–5122. https://doi.org/10.1038/onc.2012.5
E2F1	Cyclin D1	(+)	Transcriptional	E2F binding site mutations decrease the *CCND1* promoter activity.	Por, E., Byun, H. J., Lee, E. J., Lim, J. H., Jung, S. Y., Park, I., … Lee, H. (2010). The cancer/testis antigen CAGE with oncogenic potential stimulates cell proliferation by up-regulating cyclins D1 and E in an AP-1- and E2F-dependent

				E2F1 activates Cyclin D1 expression.	manner. Journal of Biological Chemistry, 285(19), 14475–14485. https://doi.org/10.1074/jbc.M109.084400
KLF4	Cyclin D1	(-)	Transcriptional	KLF4 decreases the *CCND1* promoter activity.	Shie, J.-L. (2000). Gut-enriched Kruppel-like factor represses cyclin D1 promoter activity through Sp1 motif. Nucleic Acids Research, 28(15), 2969–2976. https://doi.org/10.1093/nar/28.15.2969
miR-34a	Cyclin D1	(-)	Post-transcriptional	Cyclin D1 is a target of miR-34a.	Sun, F., Fu, H., Liu, Q., Tie, Y., Zhu, J., Xing, R., Sun, Z., & Zheng, X. (2008). Downregulation of CCND1 and CDK6 by miR-34a induces cell cycle arrest. 582, 1564–1568. https://doi.org/10.1016/j.febslet.2008.03.057
HNF6	Cyclin D1	(+)	Transcriptional	HNF6 is recruited to the *CCND1* promoter. HNF6 overexpression increases Cyclin D1 expression.	Tan, Y., Yoshida, Y., Hughes, D. E., & Costa, R. H. (2006). Increased Expression of Hepatocyte Nuclear Factor 6 Stimulates Hepatocyte Proliferation During Mouse Liver Regeneration. Gastroenterology, 130(4), 1283–1300. https://doi.org/10.1053/j.gastro.2006.01.010
β-catenin	Cyclin D1	(+)	Transcriptional	*CCND1* promoter is activated by β-catenin signaling.	Tetsu, O., & McCormick, F. (1999). β-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature, 398(6726), 422–426. https://doi.org/10.1038/18884
FOXA2	Cyclin D1	(+)	Transcriptional	FOXA2 is recruited to the *CCND1* promoter.	Villacorte, M., Suzuki, K., Hirasawa, A., Ohkawa, Y., Suyama, M., Maruyama, T., … Yamada, G. (2013). β-Catenin signaling regulates Foxa2 expression during endometrial hyperplasia formation. Oncogene, 32(29), 3477–3482. https://doi.org/10.1038/onc.2012.376
c-Myc	Cyclin D1	(+)	Transcriptional	c-Myc activates the *CCND1* promoter. C-Myc activates Cyclin D1 expression.	Yang, H., Li, T. W. H., Ko, K. S., Xia, M., & Lu, S. C. (2009). Switch from Mnt-Max to Myc-Max induces p53 and cyclin D1 expression and apoptosis during cholestasis in mouse and human hepatocytes. Hepatology, 49(3), 860–870. https://doi.org/10.1002/hep.22720 Tang, S. W., Chang, W. H., Su, Y. C., Chen, Y. C., Lai, Y. H., Wu, P. T., … Lin, J. Y. (2009). MYC pathway is activated in clear cell renal cell carcinoma and essential for proliferation of clear cell renal cell carcinoma cells. Cancer Letters, 273(1), 35–43. https://doi.org/10.1016/j.canlet.2008.07.038
E2F1	E2F1	(+)	Transcriptional	E2F1 regulates its promoter.	Hsiao, K. M., McMahon, S. L., & Farnham, P. J. (1994). Multiple DNA elements are required for the growth regulation of the mouse E2F1 promoter. Genes and Development, 8(13), 1526–1537. https://doi.org/10.1101/gad.8.13.1526 Leung, J. Y., Ehmann, G. L., Giangrande, P. H., & Nevins, J. R. (2008). A role for Myc in facilitating transcription activation by E2F1. Oncogene, 27(30), 4172–4179. https://doi.org/10.1038/onc.2008.55
YAP1	E2F1	(+)	Transcriptional	YAP1 signaling directly regulates the E2F1 expression.	Kim, W., Suk, Y., Wang, X., Park, O., Ma, X., Kim, H., Gan, W., & Jho, E. (2019). Hippo signaling is intrinsically regulated during cell cycle progression by APC / C Cdh1. 116(19). https://doi.org/10.1073/pnas.1821370116

c-Myc	E2F1	(+)	Transcriptional	c-Myc directly regulates the E2F1 expression.	Leung, J. Y., Ehmann, G. L., Giangrande, P. H., & Nevins, J. R. (2008). A role for Myc in facilitating transcription activation by E2F1. Oncogene, 27(30), 4172–4179. https://doi.org/10.1038/onc.2008.55
HNF4A	E2F1	(-)	Indirect Transcriptional	HNF4A regulates E2F1 through activation of miR-122 expression. E2F1 is a target of miR-122.	Li, Z. Y., Xi, Y., Zhu, W. N., Zeng, C., Zhang, Z. Q., Guo, Z. C., Hao, D. L., Liu, G., Feng, L., Chen, H. Z., Chen, F., Lv, X., Liu, D. P., & Liang, C. C. (2011). Positive regulation of hepatic miR-122 expression by HNF4α. Journal of hepatology, 55(3), 602–611. https://doi.org/10.1016/j.jhep.2010.12.023 Wang, B., Hsu, S. H., Wang, X., Kutay, H., Bid, H. K., Yu, J., Ganju, R. K., Jacob, S. T., Yuneva, M., & Ghoshal, K. (2014). Reciprocal regulation of microRNA-122 and c-Myc in hepatocellular cancer: role of E2F1 and transcription factor dimerization partner 2. Hepatology (Baltimore, Md.), 59(2), 555–566. https://doi.org/10.1002/hep.26712
p21	E2F1	(-)	Transcriptional	p21 downregulates E2F-dependent transcription.	Dimri, G. P., Nakanishi, M., Desprez, P. Y., Smith, J. R., & Campisi, J. (1996). Inhibition of E2F activity by the cyclin-dependent protein kinase inhibitor p21 in cells expressing or lacking a functional retinoblastoma protein. Molecular and Cellular Biology, 16(6), 2987–2997. https://doi.org/10.1128/mcb.16.6.2987 Delavaine, L., & La Thangue, N. B. (1999). Control of E2F activity by p21(Waf1/Cip1). Oncogene, 18(39), 5381–5392. https://doi.org/10.1038/sj.onc.1202923
E2F1	EED	(+)	Transcriptional	E2F1 activates the *EED* promoter.	Bracken, A. P., Pasini, D., Capra, M., Prosperini, E., Colli, E., & Helin, K. (2003). EZH2 is downstream of the pRB-E2F pathway , essential for proliferation and amplified in cancer. 22(20), 5323–5335.
c-Myc	EED	(+)	Transcriptional	c-Myc is recruited to the *Eed* promoter. Eed expression is decreased by c-Myc knockdown.	Krepelova, A., Neri, F., Maldotti, M., Rapelli, S., & Oliviero, S. (2014). Myc and Max genome-wide binding sites analysis links the Myc regulatory network with the polycomb and the core pluripotency networks in mouse embryonic stem cells. PLoS ONE, 9(2), 1–12. https://doi.org/10.1371/journal.pone.0088933 Neri, F., Zippo, A., Krepelova, A., Cherubini, A., Rocchigiani, M., & Oliviero, S. (2012). Myc Regulates the Transcription of the PRC2 Gene To Control the Expression of Developmental Genes in Embryonic Stem Cells. Molecular and Cellular Biology, 32(4), 840–851. https://doi.org/10.1128/mcb.06148-11
β-catenin	EZH2	(+)	Transcriptional	EZH2 promoter is activated by wnt/β-catenin signaling. Wnt/β-catenin signaling activates EZH2 expression.	Chen, Y., Pan, K., Wang, P., Cao, Z., Wang, W., Wang, S., … Zhang, X. (2016). HBP1-mediated regulation of p21 protein through the Mdm2/p53 and TCF4/EZH2 pathways and its impact on cell senescence and tumorigenesis. Journal of Biological Chemistry, 291(24), 12688–12705. https://doi.org/10.1074/jbc.M116.714147
c-Myc	EZH2	(+)	Transcriptional	c-Myc is recruited to the *Ezh2* promoter. EZH2	Krepelova, A., Neri, F., Maldotti, M., Rapelli, S., & Oliviero, S. (2014). Myc and Max genome-wide binding sites analysis links the Myc regulatory network with

				expression decreases by c-Myc knockdown.	the polycomb and the core pluripotency networks in mouse embryonic stem cells. PLoS ONE, 9(2), 1–12. https://doi.org/10.1371/journal.pone.0088933 Neri, F., Zippo, A., Krepelova, A., Cherubini, A., Rocchigiani, M., & Oliviero, S. (2012). Myc Regulates the Transcription of the PRC2 Gene To Control the Expression of Developmental Genes in Embryonic Stem Cells. Molecular and Cellular Biology, 32(4), 840–851. https://doi.org/10.1128/mcb.06148-11
p53	EZH2	(-)	Transcriptional	*EZH2* promoter is repressed by p53.	Tang, X., Milyavsky, M., Shats, I., Erez, N., Goldfinger, N., & Rotter, V. (2004). Activated p53 suppresses the histone methyltransferase EZH2 gene. 3, 5759–5769. https://doi.org/10.1038/sj.onc.1207706
MDM2	EZH2	(+)	Transcriptional	MDM2 associates with EZH2 and enhances the PRC2 activity.	Wienken, M., Dickmanns, A., Nemajerova, A., Kramer, D., Najafova, Z., Weiss, M., Karpiuk, O., Kassem, M., Zhang, Y., Lozano, G., Johnsen, S. A., Moll, U. M., Zhang, X., & Dobbelstein, M. (2016). MDM2 Associates with Polycomb Repressor Complex 2 and Enhances Stemness-Promoting Chromatin Modifications Independent of p53. Molecular cell, 61(1), 68–83. https://doi.org/10.1016/j.molcel.2015.12.008
SOX2	FOXA2	(-)	Transcriptional	*FOXA2* is a SOX2 target gene. SOX2 knockdown increases FOXA2 expression.	Boyer, L. A., Lee, T. I., Cole, M. F., Johnstone, S. E., Levine, S. S., Zucker, J. P., Guenther, M. G., Kumar, R. M., Murray, H. L., Jenner, R. G., Gifford, D. K., Melton, D. A., Jaenisch, R., & Young, R. A. (2005). Core Transcriptional Regulatory Circuitry in Human Embryonic Stem Cells. 122(Icm), 947–956. https://doi.org/10.1016/j.cell.2005.08.020 Kee, A., Teo, K., Arnold, S. J., Trotter, M. W. B., Brown, S., Ang, L. T., Chng, Z., Robertson, E. J., Dunn, N. R., & Vallier, L. (2011). Pluripotency factors regulate definitive endoderm specification through eomesodermin. 2, 238–250. https://doi.org/10.1101/gad.607311.allocation
miR-200a	FOXA2	(-)	Post-transcriptional	FOXA2 is a target of miR-200a.	Chen, S. ying, Ma, D. ning, Chen, Q. dan, Zhang, J. jun, Tian, Y. ru, Wang, Z. cheng, Cai, H., Lin, Y., & Sun, H. C. (2017). MicroRNA-200a inhibits cell growth and metastasis by targeting Foxa2 in hepatocellular carcinoma. Journal of Cancer, 8(4), 617–625. https://doi.org/10.7150/jca.17394
FOXA2	FOXA2	(+)	Transcriptional	FOXA2 is recruited to the *Foxa2* promoter.	Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906 Wederell, E. D., Bilenky, M., Cullum, R., Thiessen, N., Dagpinar, M., Delaney, A., … Hoodless, P. A. (2008). Global analysis of in vivo Foxa2-binding sites in mouse adult liver using massively parallel sequencing. Nucleic Acids Research, 36(14), 4549–4564. https://doi.org/10.1093/nar/gkn382
HNF4A	FOXA2	(+)	Transcriptional	HNF4a is recruited to the *Foxa2* promoter.	Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor

				Moreover, HNF4a knockdown suppresses FOXA2 expression.	network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906 Delaforest, A., Nagaoka, M., Si-tayeb, K., Noto, F. K., Konopka, G., Battle, M. A., & Duncan, S. A. (2011). HNF4A is essential for specification of hepatic progenitors from human pluripotent stem cells. 4153, 4143–4153. https://doi.org/10.1242/dev.062547
HNF6	FOXA2	(+)	Transcriptional	HNF6 is recruited to the *Foxa2* promoter. HNF6 activates the *Foxa2* promoter.	Landry, C., Clotman, F., Hioki, T., Oda, H., Picard, J. J., Lemaigre, F. P., & Rousseau, G. G. (1997). HNF-6 is expressed in endoderm derivatives and nervous system of the mouse embryo and participates to the cross-regulatory network of liver- enriched transcription factors. Developmental Biology, 192(2), 247–257. https://doi.org/10.1006/dbio.1997.8757 Rausa, F., Samadani, U., Ye, H., Lim, L., Fletcher, C. F., Jenkins, N. A., … Costa, R. H. (1997). The cut-homeodomain transcriptional activator HNF-6 is coexpressed with its target gene HNF-3β in the developing murine liver and pancreas. Developmental Biology, 192(2), 228–246. https://doi.org/10.1006/dbio.1997.8744
SOX9	FOXA2	(+)	Transcriptional	SOX9 is recruited to the *Foxa2* promoter. Sox9 knockdown decreases the FOXA2 expression.	Lynn, F. C., Smith, S. B., Wilson, M. E., Yang, K. Y., Nekrep, N., & German, M. S. (2007). Sox9 coordinates a transcriptional network in pancreatic progenitor cells. Proceedings of the National Academy of Sciences of the United States of America, 104(25), 10500–10505. https://doi.org/10.1073/pnas.0704054104
GATA6	FOXA2	(+)	Transcriptional	GATA6 activates the *FOXA2* promoter. GATA6 activates the FOXA2 expression.	Martinelli, P., Carrillo-De Santa Pau, E., Cox, T., Sainz, B., Dusetti, N., Greenhalf, W., … Real, F. X. (2017). GATA6 regulates EMT and tumour dissemination, and is a marker of response to adjuvant chemotherapy in pancreatic cancer. Gut, 66(9), 1665–1676. https://doi.org/10.1136/gutjnl-2015-311256
β-catenin	FOXA2	(+)	Transcriptional	*FOXA2* promoter is activated by β-catenin signaling.	Villacorte, M., Suzuki, K., Hirasawa, A., Ohkawa, Y., Suyama, M., Maruyama, T., … Yamada, G. (2013). β-Catenin signaling regulates Foxa2 expression during endometrial hyperplasia formation. Oncogene, 32(29), 3477–3482. https://doi.org/10.1038/onc.2012.376
TGF-β1	FOXA2	(-)	Transcriptional	TGF-β1 signaling represses the *FOXA2* transcription.	Zhang, Y., Handley, D., Kaplan, T., Yu, H., Bais, A. S., Richards, T., … Kaminski, N. (2011). High throughput determination of TGFβ1/SMAD3 targets in A549 lung epithelial cells. PLoS ONE, 6(5). https://doi.org/10.1371/journal.pone.0020319
KLF4	GATA6	(-)	Transcriptional	*Gata6* promoter is activated by Klf4 knockdown.	Aksoy, I., Giudice, V., Delahaye, E., Wianny, F., Aubry, M., Mure, M., … Savatier, P. (2014). Klf4 and Klf5 differentially inhibit mesoderm and endoderm differentiation in embryonic stem cells. Nature Communications, 5. https://doi.org/10.1038/ncomms4719
SOX2	GATA6	(+)	Transcriptional	SOX2 is recruited to the *GATA6* promoter. *SOX2* activates the *GATA6* promoter.	Ochieng, J. K., Schilders, K., Kool, H., Boerema-De Munck, A., Buscop-Van Kempen, M., Gontan, C., … Rottier, R. J. (2014). Sox2 regulates the emergence of lung basal cells by directly activating the transcription of Trp63. American Journal of Respiratory Cell and Molecular Biology, 51(2), 311–322. https://doi.org/10.1165/rcmb.2013-0419OC

NANOG	GATA6	(-)	Transcriptional	NANOG represses *GATA6* promoter.	Singh, A. M., Hamazaki, T., Hankowski, K. E., & Terada, N. (2007). A Heterogeneous Expression Pattern for Nanog in Embryonic Stem Cells. Stem Cells, 25(10), 2534–2542. https://doi.org/10.1634/stemcells.2007-0126 Hyslop, L., Stojkovic, M., Armstrong, L., Walter, T., Stojkovic, P., Przyborski, S., … Lako, M. (2005). Downregulation of NANOG Induces Differentiation of Human Embryonic Stem Cells to Extraembryonic Lineages. Stem Cells, 23(8), 1035–1043. https://doi.org/10.1634/stemcells.2005-0080
c-Myc	GATA6	(-)	Transcriptional	c-Myc is recruited to the *Gata6* promoter. Gata6 mRNA is upregulated by c-Myc knockdown.	Smith, K. N., Singh, A. M., & Dalton, S. (2010). Myc represses primitive endoderm differentiation in pluripotent stem cells. Cell Stem Cell, 7(3), 343–354. https://doi.org/10.1016/j.stem.2010.06.023
SNAI1	HNF1A	(-)	Transcriptional	Snail is recruited to the *Hnf1α* promoter. Snail overexpression downregulates HNF1a expression.	Battistelli, C., Cicchini, C., Santangelo, L., Tramontano, A., Grassi, L., Gonzalez, F. J., … Tripodi, M. (2017). The Snail repressor recruits EZH2 to specific genomic sites through the enrollment of the lncRNA HOTAIR in epithelial-to-mesenchymal transition. Oncogene, 36(7), 942–955. https://doi.org/10.1038/onc.2016.260
HNF4A	HNF1A	(+)	Transcriptional	HNF4a is recruited to the *Hnf1a* promoter. Moreover, HNF4a positively regulates HNF1a expression.	Kuo, C. J., Conley, P. B., Chen, L., Sladek, F. M., Darnell, J. E., & Crabtree, G. R. (1992). A transcriptional hierarchy involved in mammalian cell-type specification. Nature, 355(6359), 457–461. https://doi.org/10.1038/355457a0 Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906
FOXA2	HNF1A	(+)	Transcriptional	FOXA2 activates the *HNF1A* promoter.	Miura, H., Tomaru, Y., Nakanishi, M., Kondo, S., Hayashizaki, Y., & Suzuki, M. (2009). Identification of DNA regions and a set of transcriptional regulatory factors involved in transcriptional regulation of several human liver-enriched transcription factor genes. Nucleic Acids Research, 37(3), 778–792. https://doi.org/10.1093/nar/gkn978 Kuo, C. J., Conley, P. B., Chen, L., Sladek, F. M., Darnell, J. E., & Crabtree, G. R. (1992). A transcriptional hierarchy involved in mammalian cell-type specification. Nature, 355(6359), 457–461. https://doi.org/10.1038/355457a0
HNF1A	HNF1A	(+)	Transcriptional	HNF1A activates the *HNF1A* promoter.	Miura, H., Tomaru, Y., Nakanishi, M., Kondo, S., Hayashizaki, Y., & Suzuki, M. (2009). Identification of DNA regions and a set of transcriptional regulatory factors involved in transcriptional regulation of several human liver-enriched transcription factor genes. Nucleic Acids Research, 37(3), 778–792. https://doi.org/10.1093/nar/gkn978 Minra, N., & Tanaka, K. (1993). Analysis of the rat hepatocyte nuclear factor (HNF) 1 gene promoter: Synergistic

					activation by HNF4 and HNF1 proteins. Nucleic Acids Research, 21(16), 3731–3736. https://doi.org/10.1093/nar/21.16.3731
NF-κB	HNF1A	(-)	Indirect transcriptional	NF-κB downregulates the HNF1a expression through miR-21 and miR-146a	Qian, H., Deng, X., Huang, Z., Wei, J., Ding, C., Feng, R., & Zeng, X. (2015). An HNF1 α -regulated feedback circuit modulates hepatic fibrogenesis via the crosstalk between hepatocytes and hepatic stellate cells. Nature Publishing Group, 25(8), 930–945. https://doi.org/10.1038/cr.2015.84
FOXA2	HNF4A	(+)	Transcriptional	FOXA2 activates the *Hnf4a* promoter.	Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906 Duncan, S. A., Navas, M. A., Dufort, D., Rossant, J., & Stoffel, M. (1998). Regulation of a transcription factor network required for differentiation and metabolism. Science, 281(5377), 692–695. https://doi.org/10.1126/science.281.5377.692
HNF1A	HNF4A	(+)	Transcriptional	HNF1a is recruited to the *Hnf4a* promoter. HNF1a expression positively correlates with HNF4a expression.	Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906
HNF4A	HNF4A	(+)	Transcriptional	HNF4A activates the *HNF4A* promoter.	Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906 Hatzis, P., & Talianidis, I. (2001). Regulatory Mechanisms Controlling Human Hepatocyte Nuclear Factor 4α Gene Expression. Molecular and Cellular Biology, 21(21), 7320–7330. https://doi.org/10.1128/mcb.21.21.7320-7330.2001
HNF6	HNF4A	(+)	Transcriptional	HNF6 is recruited to the *Hnf4a* promoter. HNF6 activates the *Hnf4a* promoter.	Landry, C., Clotman, F., Hioki, T., Oda, H., Picard, J. J., Lemaigre, F. P., & Rousseau, G. G. (1997). HNF-6 is expressed in endoderm derivatives and nervous system of the mouse embryo and participates to the cross-regulatory network of liver- enriched transcription factors. Developmental Biology, 192(2), 247–257. https://doi.org/10.1006/dbio.1997.8757 Rausa, F., Samadani, U., Ye, H., Lim, L., Fletcher, C. F., Jenkins, N. A., … Costa, R. H. (1997). The cut-homeodomain transcriptional activator HNF-6 is coexpressed with its target gene HNF-3β in the developing murine liver and pancreas. Developmental Biology, 192(2), 228–246. https://doi.org/10.1006/dbio.1997.8744
p53	HNF4A	(-)	Transcriptional	p53 downregulates the *HNF4A* transcription.	Maeda, Y., Hwang-Verslues, W. W., Wei, G., Fukazawa, T., Durbin, M. L., Owen, L. B., Liu, X., & Sladek, F. M. (2006). Tumour suppressor p53 down-regulates the expression of the human hepatocyte nuclear factor 4α (HNF4α) gene. Biochemical Journal, 400(2), 303–313. https://doi.org/10.1042/BJ20060614

GATA6	HNF4A	(+)	Transcriptional	GATA6 activates the *HNF4A* promoter.	Morrisey, E. E., Tang, Z., Sigrist, K., Lu, M. M., Jiang, F., Ip, H. S., & Parmacek, M. S. (1998). GATA6 regulates HNF4 and is required for differentiation of visceral endoderm in the mouse embryo. Genes and Development, 12(22), 3579–3590. https://doi.org/10.1101/gad.12.22.3579 Hatzis, P., & Talianidis, I. (2001). Regulatory Mechanisms Controlling Human Hepatocyte Nuclear Factor 4α Gene Expression. Molecular and Cellular Biology, 21(21), 7320–7330. https://doi.org/10.1128/mcb.21.21.7320-7330.2001
NF-κB	HNF4A	(-)	Indirect transcriptional	NF-κB downregulates the HNF4A expression through miR-21 upregulation.	Ning, B., Ding, J., Liu, J., Yin, C., Xu, W., Cong, W., Zhang, Q., Chen, F., Han, T., Deng, X., Wang, P., Jiang, C., Zhang, J., Zhang, X., Wang, H., & Xie, W. (2014). Feedback Circuit Modulates Liver Cancer Progression. 81230011. https://doi.org/10.1002/hep.27177
YAP1	HNF4A	(-)	Transcriptional	YAP1 is recruited to the *HNF4A* promoter. YAP1 represses HNF4A expression.	Noce, V., Battistelli, C., Cozzolino, A. M., Consalvi, V., Cicchini, C., Strippoli, R., … Amicone, L. (2019). YAP integrates the regulatory Snail/HNF4α circuitry controlling epithelial/hepatocyte differentiation. Cell Death and Disease, 10(10). https://doi.org/10.1038/s41419-019-2000-8 Lee, D. H., Park, J. O., Kim, T. S., Kim, S. K., Kim, T. H., Kim, M. C., … Lim, D. S. (2016). LATS-YAP/TAZ controls lineage specification by regulating TGFβ signaling and Hnf4α expression during liver development. Nature Communications, 7(May), 1–14. https://doi.org/10.1038/ncomms11961
SNAI1	HNF4A	(-)	Transcriptional	SNAI1 is recruited to the *HNF4A* promoter. SNAI1 overexpression downregulates HNF4A expression.	Yang, M., Li, S. N., Anjum, K. M., Gui, L. X., Zhu, S. S., Liu, J., … Li, B. A. (2013). A double-negative feedback loop between Wnt-β-catenin signaling and HNF4α regulates epithelial-mesenchymal transition in hepatocellular carcinoma. Journal of Cell Science, 126(24), 5692–5703. https://doi.org/10.1242/jcs.135053 Battistelli, C., Cicchini, C., Santangelo, L., Tramontano, A., Grassi, L., Gonzalez, F. J., … Tripodi, M. (2017). The Snail repressor recruits EZH2 to specific genomic sites through the enrollment of the lncRNA HOTAIR in epithelial-to-mesenchymal transition. Oncogene, 36(7), 942–955. https://doi.org/10.1038/onc.2016.260
SNAI2	HNF4A	(-)	Transcriptional	SNAI2 is recruited on the *HNF4A* promoter. SNAI2 overexpression downregulates HNF4A expression.	Yang, M., Li, S. N., Anjum, K. M., Gui, L. X., Zhu, S. S., Liu, J., … Li, B. A. (2013). A double-negative feedback loop between Wnt-β-catenin signaling and HNF4α regulates epithelial-mesenchymal transition in hepatocellular carcinoma. Journal of Cell Science, 126(24), 5692–5703. https://doi.org/10.1242/jcs.135053
OCT4	HNF6	(-)	Transcriptional	*HNF6* is an OCT4 target gene.	Boyer, L. A., Lee, T. I., Cole, M. F., Johnstone, S. E., Levine, S. S., Zucker, J. P., Guenther, M. G., Kumar, R. M., Murray, H. L., Jenner, R. G., Gifford, D. K., Melton, D. A., Jaenisch, R., & Young, R. A. (2005). Core Transcriptional Regulatory Circuitry in Human Embryonic Stem Cells. 122(Icm), 947–956. https://doi.org/10.1016/j.cell.2005.08.020

SOX2	HNF6	(-)	Transcriptional	*HNF6* is a SOX2 target gene.	Boyer, L. A., Lee, T. I., Cole, M. F., Johnstone, S. E., Levine, S. S., Zucker, J. P., Guenther, M. G., Kumar, R. M., Murray, H. L., Jenner, R. G., Gifford, D. K., Melton, D. A., Jaenisch, R., & Young, R. A. (2005). Core Transcriptional Regulatory Circuitry in Human Embryonic Stem Cells. 122(Icm), 947–956. https://doi.org/10.1016/j.cell.2005.08.020
NANOG	HNF6	(-)	Transcriptional	*HNF6* is a NANOG target gene.	Boyer, L. A., Lee, T. I., Cole, M. F., Johnstone, S. E., Levine, S. S., Zucker, J. P., Guenther, M. G., Kumar, R. M., Murray, H. L., Jenner, R. G., Gifford, D. K., Melton, D. A., Jaenisch, R., & Young, R. A. (2005). Core Transcriptional Regulatory Circuitry in Human Embryonic Stem Cells. 122(Icm), 947–956. https://doi.org/10.1016/j.cell.2005.08.020
HNF1A	HNF6	(+)	Transcriptional	HNF1a is recruited to the *Hnf6* promoter. HNF1a activates HNF6 expression.	Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906
HNF4A	HNF6	(+)	Transcriptional	HNF4a binds to the *Hnf6* promoter. HNF4a activates the *Hnf6* promoter.	Lahuna, O., Rastegar, M., Maiter, D., Thissen, J. P., Lemaigre, F. P., & Rousseau, G. G. (2000). Involvement of STAT5 (signal transducer and activator of transcription 5) and HNF-4 (hepatocyte nuclear factor 4) in the transcriptional control of the hnf6 gene by growth hormone. Molecular Endocrinology, 14(2), 285–294. https://doi.org/10.1210/mend.14.2.0423 Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906
SOX9	HNF6	(+)	Transcriptional	SOX9 is recruited to the *Hnf6* promoter. SOX9 knockdown decreases the HNF6 expression.	Lynn, F. C., Smith, S. B., Wilson, M. E., Yang, K. Y., Nekrep, N., & German, M. S. (2007). Sox9 coordinates a transcriptional network in pancreatic progenitor cells. Proceedings of the National Academy of Sciences of the United States of America, 104(25), 10500–10505. https://doi.org/10.1073/pnas.0704054104
KLF4	HNF6	(+)	Transcriptional	KLF4 activates the *HNF6* promoter. KLF4 activates HNF6 expression.	Sun, H., Tang, H., Xie, D., Jia, Z., Ma, Z., Wei, D., Mishra, L., Gao, Y., Zheng, S., Xie, K., & Peng, Z. (2016). Krüppel-like Factor 4 Blocks Hepatocellular Carcinoma Dedifferentiation and Progression through Activation of Hepatocyte Nuclear Factor-6. Clinical cancer research : an official journal of the American Association for Cancer Research, 22(2), 502–512. https://doi.org/10.1158/1078-0432.CCR-15-0528
HNF6	HNF6	(+)	Transcriptional	HNF6 activates its promoter. HNF6 overexpression increases the endogenous HNF6 expression.	Tan, Y., Yoshida, Y., Hughes, D. E., & Costa, R. H. (2006). Increased Expression of Hepatocyte Nuclear Factor 6 Stimulates Hepatocyte Proliferation During Mouse Liver Regeneration. Gastroenterology, 130(4), 1283–1300. https://doi.org/10.1053/j.gastro.2006.01.010 Kyrmizi, I., Hatzis, P., Katrakili, N., Tronche, F., Gonzalez, F. J., & Talianidis, I. (2006). Plasticity and expanding

					complexity of the hepatic transcription factor network during liver development. Genes and Development, 20(16), 2293–2305. https://doi.org/10.1101/gad.390906
NF-κB	IkB	(+)	Transcriptional	NF-κB directly activates the *IkB* transcription.	Algarté, M., Kwon, H., Génin, P., & Hiscott, J. (1999). Identification by in vivo genomic footprinting of a transcriptional switch containing NF-kappaB and Sp1 that regulates the IkappaBalpha promoter. Molecular and cellular biology, 19(9), 6140–6153. https://doi.org/10.1128/mcb.19.9.6140
YAP1	IL_6	(+)	Transcriptional	YAP1 activates the expression of IL_6.	Kim, T., Yang, S. J., Hwang, D., Song, J., Kim, M., Kyum Kim, S., Kang, K., Ahn, J., Lee, D., Kim, M. Y., Kim, S., Seung Koo, J., Seok Koh, S., Kim, S. Y., & Lim, D. S. (2015). A basal-like breast cancer-specific role for SRF-IL6 in YAP-induced cancer stemness. Nature communications, 6, 10186. https://doi.org/10.1038/ncomms10186 Gao, Y., Yang, Y., Yuan, F., Huang, J., Xu, W., Mao, B., Yuan, Z., & Bi, W. (2017). ORIGINAL ARTICLE TNF α - YAP / p65-HK2 axis mediates breast cancer cell migration. May. https://doi.org/10.1038/oncsis.2017.83
FOXA2	IL_6	(-)	Transcriptional	FOXA1/2 directly regulates IL_6 at the transcriptional level.	Li, Z., White, P., Tuteja, G., Rubins, N., Sackett, S., & Kaestner, K. H. (2009). Foxa1 and Foxa2 regulate bile duct development in mice. 119(6). https://doi.org/10.1172/JCI38201.by
KLF4	IL_6	(+)	Transcriptional	KLF4 directly activates the IL-6 expression.	Luo, X., Chen, J., Ruan, J., Chen, Y., Mo, X., Xie, J., & Lv, G. (2016). Krüppel-Like Factor 4 Is a Regulator of Proinflammatory Signaling in Fibroblast-Like Synoviocytes through Increased IL-6 Expression. Mediators of inflammation, 2016, 1062586. https://doi.org/10.1155/2016/1062586
SNAI1	IL_6	(+)	Transcriptional	SNAI1 activates the IL_6 expression.	Peng, C. Y., Liao, Y. W., Lu, M. Y., Yang, C. M., Hsieh, P. L., & Yu, C. C. (2020). Positive Feedback Loop of SNAIL-IL-6 Mediates Myofibroblastic Differentiation Activity in Precancerous Oral Submucous Fibrosis. Cancers, 12(6), 1611. https://doi.org/10.3390/cancers12061611
TWIST1	IL_6	(-)	Transcriptional	TWIST1 directly represses the IL-6 expression.	Pettersson, A. T., Laurencikiene, J., Mejhert, N., Näslund, E., Bouloumié, A., Dahlman, I., Arner, P., & Rydén, M. (2010). A possible inflammatory role of twist1 in human white adipocytes. Diabetes, 59(3), 564–571. https://doi.org/10.2337/db09-0997
NANOG	KLF4	(+)	Transcriptional	NANOG activates KLF4 expression.	Bourillot, P.-Y., Aksoy, I., Schreiber, V., Wianny, F., Schulz, H., Hummel, O., Hubner, N., & Savatier, P. (2009). Novel STAT3 target genes exert distinct roles in the inhibition of mesoderm and endoderm differentiation in cooperation with Nanog. Stem Cells (Dayton, Ohio), 27(8), 1760–1771. https://doi.org/10.1002/stem.110 Chen, X., Xu, H., Yuan, P., Fang, F., Huss, M., Vega, V. B., Wong, E., Orlov, Y. L., Zhang, W., Jiang, J., Loh, Y., Yeo, H. C., Yeo, Z. X., Narang, V., Govindarajan, K. R., Leong, B., Shahab, A., Ruan, Y., Bourque, G., … Ng, H. (2008). Resource Integration of External Signaling

					Pathways with the Core Transcriptional Network in Embryonic Stem Cells. 1106–1117. https://doi.org/10.1016/j.cell.2008.04.043
miR-34a	KLF4	(-)	Post-transcriptional	KLF4 is a target of miR-34a.	Chen, Q., Li, L., Tu, Y., Zheng, L. L., Liu, W., Zuo, X. Y., He, Y. M., Zhang, S. Y., Zhu, W., Cao, J. P., Cui, F. M., & Hou, J. (2014). MiR-34a regulates apoptosis in liver cells by targeting the KLF4 gene. Cellular and Molecular Biology Letters, 19(1), 52–64. https://doi.org/10.2478/s11658-013-0115-y
SOX9	KLF4	(-)	Transcriptional	SOX9 downregulates the KLF4 expression.	Flandez, M., Guilmeau, S., Blache, P., & Augenlicht, L. H. (2008). KLF4 regulation in intestinal epithelial cell maturation. Experimental Cell Research, 314(20), 3712–3723. https://doi.org/10.1016/j.yexcr.2008.10.004
SNAI2	KLF4	(-)	Transcriptional	SNAI2 is recruited to the *Klf4* promoter.	Liu, Y.-N., Abou-Kheir, W., Yin, J. J., Fang, L., Hynes, P., Casey, O., … Kelly, K. (2012). Critical and Reciprocal Regulation of KLF4 and SLUG in Transforming Growth Factor -Initiated Prostate Cancer Epithelial-Mesenchymal Transition. Molecular and Cellular Biology, 32(5), 941–953. https://doi.org/10.1128/mcb.06306-11
p53	KLF4	(+)	Transcriptional	p53 activates the *Klf4* promoter.	Zhang, W., Geiman, D. E., Shields, J. M., Dang, D. T., Mahatan, C. S., Kaestner, K. H., Biggs, J. R., Kraft, A. S., & Yang, V. W. (2000). The Gut-enriched Kru ¨ ppel-like Factor (Krüppel-like Factor 4) Mediates the Transactivating Effect of p53 on the p21 WAF1 / Cip1 Promoter *. 275(24), 18391–18398. https://doi.org/10.1074/jbc.C000062200
p16	MDM2	(-)	Post-transcriptional	p16 represses MDM2 through miRNAs.	Al-Khalaf, H. H., & Aboussekhra, A. (2018). p16 Controls p53 Protein Expression Through miR-dependent Destabilization of MDM2. Molecular cancer research : MCR, 16(8), 1299–1308. https://doi.org/10.1158/1541-7786.MCR-18-0017
TGF-β1	MDM2	(+)	Transcriptional	TGF-β1 signaling activates the MDM2 expression.	Araki, S., Eitel, J. A., Batuello, C. N., Bijangi-Vishehsaraei, K., Xie, X. J., Danielpour, D., Pollok, K. E., Boothman, D. A., & Mayo, L. D. (2010). TGF-β1-induced expression of human Mdm2 correlates with late-stage metastatic breast cancer. Journal of Clinical Investigation, 120(1), 290–302. https://doi.org/10.1172/JCI39194
p53	MDM2	(+)	Transcriptional	p53 directly activates the M*dm2* transcription.	Barak, Y., Gottlieb, E., Juven-Gershon, T., & Oren, M. (1994). Regulation of mdm2 expression by p53: Alternative promoters produce transcripts with nonidentical translation potential. Genes and Development, 8(15), 1739–1749. https://doi.org/10.1101/gad.8.15.1739
NF-κB	MDM2	(+)	Transcriptional	NF-κB directly activates the *MDM2* transcription.	Busuttil, V., Droin, N., McCormick, L., Bernassol, F., Candi, E., Melino, G., & Green, D. R. (2010). NF-κB inhibits T-cell activation-induced, p73-dependent cell death by induction of MDM2. Proceedings of the National Academy of Sciences of the United States of America, 107(42), 18061–18066. https://doi.org/10.1073/pnas.1006163107
ZEB1	miR-200a,b	(-)	Transcriptional	ZEB1 represses mir-200a,b expression.	Bracken, C. P., Gregory, P. A., Kolesnikoff, N., Bert, A. G., Wang, J., Shannon, M. F., & Goodall, G. J. (2008). A double-negative feedback loop between ZEB1-SIP1

					and the microRNA-200 family regulates epithelial-mesenchymal transition. *Cancer Research*, *68*(19), 7846–7854. https://doi.org/10.1158/0008-5472.CAN-08-1942
SOX2	miR-200a,b	(+)	Transcriptional	SOX2 activates the miR-200a,b expression.	Wang, G., Guo, X., Hong, W., Liu, Q., Wei, T., Lu, C., Gao, L., Ye, D., Zhou, Y., Chen, J., Wang, J., Wu, M., Liu, H., & Kang, J. (2013). Critical regulation of miR-200/ZEB2 pathway in Oct4/Sox2-induced mesenchymal-to-epithelial transition and induced pluripotent stem cell generation. Proceedings of the National Academy of Sciences of the United States of America, 110(8), 2858–2863. https://doi.org/10.1073/pnas.1212769110
HNF4A	miR-200a,b,c	(+)	Transcriptional	HNF4a activates the expression of miR-200a, b, c.	Garibaldi, F., Cicchini, C., Conigliaro, A., Santangelo, L., Cozzolino, A. M., Grassi, G., Marchetti, A., Tripodi, M., & Amicone, L. (2012). An epistatic mini-circuitry between the transcription factors Snail and HNF4α controls liver stem cell and hepatocyte features exhorting opposite regulation on stemness-inhibiting microRNAs. Cell Death and Differentiation, 19(6), 937–946. https://doi.org/10.1038/cdd.2011.175
SNAI2	miR-200b	(-)	Transcriptional	SNAI2 represses miR-200b expresssion.	Liu, Y., Yin, J. J., Hynes, P. G., Casey, O. M., Fang, L., Yi, M., Stephens, R. M., Seng, V., & Martin, P. (2013). MiR-1 and miR-200 inhibit EMT via Slug -dependent and tumorigenesis via Slug -independent mechanisms. January 2012, 296–306. https://doi.org/10.1038/onc.2012.58
ZEB1	miR-200c	(-)	Transcriptional	ZEB1 represses the miR-200c expression.	Burk, U., Schubert, J., Wellner, U., Schmalhofer, O., Vincan, E., Spaderna, S., & Brabletz, T. (2008). A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. EMBO Reports, 9(6), 582–589. https://doi.org/10.1038/embor.2008.74
p53	miR-200c	(+)	Transcriptional	p53 activates the miR-200c expression.	Chang, C. J., Chao, C. H., Xia, W., Yang, J. Y., Xiong, Y., Li, C. W., Yu, W. H., Rehman, S. K., Hsu, J. L., Lee, H. H., Liu, M., Chen, C. Te, Yu, D., & Hung, M. C. (2011). P53 regulates epithelial-mesenchymal transition and stem cell properties through modulating miRNAs. Nature Cell Biology, 13(3), 317–323. https://doi.org/10.1038/ncb2173
BMI1	miR-200c	(-)	Transcriptional	BMI1 represses the miR-200c expression.	Dimri, M., Kang, M., & Dimri, G. P. (2016). A miR-200c/141-BMI1 autoregulatory loop regulates oncogenic activity of BMI1 in cancer cells. Oncotarget, 7(24), 36220–36234. https://doi.org/10.18632/oncotarget.8811
SNAI1	miR-200c	(-)	Transcriptional	SNAI1 represses the miR-200c expression.	Garibaldi, F., Cicchini, C., Conigliaro, A., Santangelo, L., Cozzolino, A. M., Grassi, G., Marchetti, A., Tripodi, M., & Amicone, L. (2012). An epistatic mini-circuitry between the transcription factors Snail and HNF4α controls liver stem cell and hepatocyte features exhorting opposite regulation on stemness-inhibiting microRNAs. Cell Death and Differentiation, 19(6), 937–946. https://doi.org/10.1038/cdd.2011.175 Gill, J. G., Langer, E. M., Lindsley, R. C., Cai, M., Murphy, T. L., Kyba, M., & Murphy, K. M. (2011). Snail

					and the microRNA-200 family act in opposition to regulate epithelial-to-mesenchymal transition and germ layer fate restriction in differentiating ESCs. Stem cells (Dayton, Ohio), 29(5), 764–776. https://doi.org/10.1002/stem.628
OCT4	miR-200c	(+)	Transcriptional	OCT4 activates the miR-200c expression.	Wang, G., Guo, X., Hong, W., Liu, Q., Wei, T., Lu, C., Gao, L., Ye, D., Zhou, Y., Chen, J., Wang, J., Wu, M., Liu, H., & Kang, J. (2013). Critical regulation of miR-200/ZEB2 pathway in Oct4/Sox2-induced mesenchymal-to-epithelial transition and induced pluripotent stem cell generation. Proceedings of the National Academy of Sciences of the United States of America, 110(8), 2858–2863. https://doi.org/10.1073/pnas.1212769110
p53	miR-34a	(-)	Transcriptional	p53 activates the miR-34a expression.	Bommer, G. T., Gerin, I., Feng, Y., Kaczorowski, A. J., Kuick, R., Love, R. E., Zhai, Y., Giordano, T. J., Qin, Z. S., Moore, B. B., MacDougald, O. A., Cho, K. R., & Fearon, E. R. (2007). p53-mediated activation of miRNA34 candidate tumor-suppressor genes. Current biology : CB, 17(15), 1298–1307.
HNF4a	miR-34a	(+)	Transcriptional	HNF4a activates the miR-34a expression.	Garibaldi, F., Cicchini, C., Conigliaro, A., Santangelo, L., Cozzolino, A. M., Grassi, G., Marchetti, A., Tripodi, M., & Amicone, L. (2012). An epistatic mini-circuitry between the transcription factors Snail and HNF4α controls liver stem cell and hepatocyte features exhorting opposite regulation on stemness-inhibiting microRNAs. Cell Death and Differentiation, 19(6), 937–946. https://doi.org/10.1038/cdd.2011.175
SNAI1	miR-34a	(-)	Transcriptional	SNAI1 represses the miR-34a expression.	Garibaldi, F., Cicchini, C., Conigliaro, A., Santangelo, L., Cozzolino, A. M., Grassi, G., Marchetti, A., Tripodi, M., & Amicone, L. (2012). An epistatic mini-circuitry between the transcription factors Snail and HNF4α controls liver stem cell and hepatocyte features exhorting opposite regulation on stemness-inhibiting microRNAs. Cell Death and Differentiation, 19(6), 937–946. https://doi.org/10.1038/cdd.2011.175 Siemens, H., Jackstadt, R., Hünten, S., Kaller, M., Menssen, A., Götz, U., & Hermeking, H. (2011). miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. Cell cycle (Georgetown, Tex.), 10(24), 4256–4271. https://doi.org/10.4161/cc.10.24.18552
ZEB1	miR-34a	(-)	Transcriptional	ZEB1 represses the miR-34a expression.	Siemens, H., Jackstadt, R., Hünten, S., Kaller, M., Menssen, A., Götz, U., & Hermeking, H. (2011). miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. Cell cycle (Georgetown, Tex.), 10(24), 4256–4271. https://doi.org/10.4161/cc.10.24.18552 Ahn, Y. H., Gibbons, D. L., Chakravarti, D., Creighton, C. J., Rizvi, Z. H., Adams, H. P., Pertsemlidis, A., Gregory, P. A., Wright, J. A., Goodall, G. J., Flores, E. R., & Kurie, J. M. (2012). ZEB1 drives prometastatic actin cytoskeletal remodeling by downregulating miR-34a expression. The Journal of clinical investigation, 122(9), 3170–3183. https://doi.org/10.1172/JCI63608

KLF4	NANOG	(+)	Transcriptional	KLF4 binds to the *NANOG* promoter. KLF4 activates NANOG expression.	Chan, K. K. K., Zhang, J., Chia, N. Y., Chan, Y. S., Sim, H. S., Tan, K. S., … Choo, A. B. H. (2009). KLF4 and PBX1 directly regulate NANOG expression in human embryonic stem cells. Stem Cells, 27(9), 2114–2125. https://doi.org/10.1002/stem.143 Jiang, J., Chan, Y. S., Loh, Y. H., Cai, J., Tong, G. Q., Lim, C. A., … Ng, H. H. (2008). A core Klf circuitry regulates self-renewal of embryonic stem cells. Nature Cell Biology, 10(3), 353–360. https://doi.org/10.1038/ncb1698
miR-34a	NANOG	(-)	Post-transcriptional	NANOG is a target of miR-34a.	Choi, Y. J., Lin, C., Ho, J. J., He, X., Okada, N., Bu, P., Zhong, Y., Kim, S. Y., Bennett, M. J., Chen, C., Ozturk, A., Hicks, G. G., Hannon, G. J., & He, L. (2011). miR-34 miRNAs provide a barrier for somatic cell reprogramming. Nature Cell Biology, 13(11). https://doi.org/10.1038/ncb2366
NANOG	NANOG	(+)	Transcriptional	NANOG is recruited to the *NANOG* promoter.	Das, S. (2012). Transcriptional Regulation of Human NANOG by Alternate Promoters in Embryonic Stem Cells. Journal of Stem Cell Research & Therapy, 01(S10). https://doi.org/10.4172/2157-7633.s10-009
SNAI1	NANOG	(-)	Transcriptional	SNAI1 regulates *Nanog* by direct binding to its promoter.	Galvagni, F., Lentucci, C., Neri, F., Dettori, D., De Clemente, C., Orlandini, M., Anselmi, F., Rapelli, S., Grillo, M., Borghi, S., & Oliviero, S. (2015). Snai1 promotes ESC exit from the pluripotency by direct repression of self-renewal genes. Stem Cells (Dayton, Ohio), 33(3), 742–750. https://doi.org/10.1002/stem.1898
NF-κB	NANOG	(+)	Transcriptional	NF-κB activates the *NANOG* promoter.	Liu, M., Sakamaki, T., Casimiro, M. C., Willmarth, N. E., Quong, A. A., Ju, X., Ojeifo, J., Jiao, X., Yeow, W. S., Katiyar, S., Shirley, L. A., Joyce, D., Lisanti, M. P., Albanese, C., & Pestell, R. G. (2010). The canonical NF-κB pathway governs mammary tumorigenesis in transgenic mice and tumor stem cell expansion. Cancer Research, 70(24), 10464–10473. https://doi.org/10.1158/0008-5472.CAN-10-0732 Takase, O., Yoshikawa, M., Idei, M., Hirahashi, J., Fujita, T., Takato, T., Isagawa, T., Nagae, G., Suemori, H., Aburatani, H., & Hishikawa, K. (2013). The Role of NF-κB Signaling in the Maintenance of Pluripotency of Human Induced Pluripotent Stem Cells. PLoS ONE, 8(2), 1–9. https://doi.org/10.1371/journal.pone.0056399
p53	NANOG	(-)	Transcriptional	p53 represses the NANOG expression.	Mohamed, E., & Tooyama, I. (2014). Biochemical and Biophysical Research Communications Knockdown of p53 suppresses Nanog expression in embryonic stem cells. Biochemical and Biophysical Research Communications, 443(2), 652–657. https://doi.org/10.1016/j.bbrc.2013.12.030 Li, M., He, Y., Dubois, W., Wu, X., Shi, J., & Huang, J. (2012). Article Distinct Regulatory Mechanisms and Functions for p53-Activated and p53-Repressed DNA Damage Response Genes in Embryonic Stem Cells. Molecular Cell, 46(1), 30–42. https://doi.org/10.1016/j.molcel.2012.01.020

OCT4	NANOG	(+)	Transcriptional	OCT4 binds to the *NANOG* promoter. OCT4 knockdown decreases the *NANOG* promoter activity.	Rodda, D. J., Chew, J. L., Lim, L. H., Loh, Y. H., Wang, B., Ng, H. H., & Robson, P. (2005). Transcriptional regulation of Nanog by OCT4 and SOX2. Journal of Biological Chemistry, 280(26), 24731–24737. https://doi.org/10.1074/jbc.M502573200
SOX2	NANOG	(+)	Transcriptional	SOX2 is recruited to the *NANOG* promoter. SOX2 knockdown decreases the *NANOG* promoter activity.	Rodda, D. J., Chew, J. L., Lim, L. H., Loh, Y. H., Wang, B., Ng, H. H., & Robson, P. (2005). Transcriptional regulation of Nanog by OCT4 and SOX2. Journal of Biological Chemistry, 280(26), 24731–24737. https://doi.org/10.1074/jbc.M502573200
GATA6	NANOG	(-)	Transcriptional	NANOG expression is downregulated by GATA6 overexpression.	Wamaitha, S. E., del Valle, I., Cho, L. T. Y., Wei, Y., Fogarty, N. M. E., Blakeley, P., … Niakan, K. K. (2015). Gata6 potently initiates reprograming of pluripotent and differentiated cells to extraembryonic endoderm stem cells. Genes and Development, 29(12), 1239–1255. https://doi.org/10.1101/gad.257071.114
TGF-β1	NANOG	(+)	Transcriptional	TGF-β1 signaling activates the *NANOG* promoter.	Xu, R. H., Sampsell-Barron, T. L., Gu, F., Root, S., Peck, R. M., Pan, G., Yu, J., Antosiewicz-Bourget, J., Tian, S., Stewart, R., & Thomson, J. A. (2008). NANOG Is a Direct Target of TGFβ/Activin-Mediated SMAD Signaling in Human ESCs. Cell Stem Cell, 3(2), 196–206. https://doi.org/10.1016/j.stem.2008.07.001
HNF1A	NF-κB	(-)	Indirect transcriptional	HNF1A inhibits the NF-κB transcriptional activity through miR-194.	Bao, C., Li, Y., Huan, L., Zhang, Y., Zhao, F., Wang, Q., Liang, L., Ding, J., Liu, L., Chen, T., Li, J., & Yao, M. (2015). NF-kB signaling relieves negative regulation by miR-194 in hepatocellular carcinoma by suppressing the transcription factor HNF-1 a. 8(387), 1–9.
HNF4A	NF-κB	(-)	Indirect transcriptional	HNF4A inhibits the NF-κB activity through miR-7 and miR-124.	Ning, B., Ding, J., Liu, J., Yin, C., Xu, W., Cong, W., Zhang, Q., Chen, F., Han, T., Deng, X., Wang, P., Jiang, C., Zhang, J., Zhang, X., Wang, H., & Xie, W. (2014). Feedback Circuit Modulates Liver Cancer Progression. 81230011. https://doi.org/10.1002/hep.27177
p53	NF-κB	(-)	Transcriptional	p53 negatively regulates NF-κB signaling.	Webster, G. A., & Perkins, N. D. (1999). Transcriptional Cross Talk between NF-κB and p53. Molecular and Cellular Biology, 19(5), 3485–3495. https://doi.org/10.1128/mcb.19.5.3485 Shao, J., Fujiwara, T., Kadowaki, Y., Fukazawa, T., Waku, T., Itoshima, T., Yamatsuji, T., Nishizaki, M., Roth, J. A., & Tanaka, N. (2000). Overexpression of the wild-type p53 gene inhibits NF-κB activity and synergizes with aspirin to induce apoptosis in human colon cancer cells. Oncogene, 19(6), 726–736. https://doi.org/10.1038/sj.onc.1203383
KLF4	OCT4	(+)	Transcriptional	KLF4 activates OCT4 expression.	Chen, X., Xu, H., Yuan, P., Fang, F., Huss, M., Vega, V. B., Wong, E., Orlov, Y. L., Zhang, W., Jiang, J., Loh, Y., Yeo, H. C., Yeo, Z. X., Narang, V., Govindarajan, K. R., Leong, B., Shahab, A., Ruan, Y., Bourque, G., … Ng, H. (2008). Resource Integration of External Signaling Pathways with the Core Transcriptional

					Network in Embryonic Stem Cells. 1106–1117. https://doi.org/10.1016/j.cell.2008.04.043
OCT4	OCT4	(+)	Transcriptional	OCT4 is recruited to the *OCT4* promoter. OCT4 knockdown decreases the *OCT4* promoter activity.	Chew, J., Tam, W., Yeap, L., Li, P., Ang, Y., Lim, B., … Ng, H. (2005). Reciprocal Transcriptional Regulation of. Society, 25(14), 6031–6046. https://doi.org/10.1128/MCB.25.14.6031
SOX2	OCT4	(+)	Transcriptional	SOX2 binds to the *OCT4* promoter. SOX2 knockdown decreases the *OCT4* promoter activity.	Chew, J., Tam, W., Yeap, L., Li, P., Ang, Y., Lim, B., … Ng, H. (2005). Reciprocal Transcriptional Regulation of. Society, 25(14), 6031–6046. https://doi.org/10.1128/MCB.25.14.6031
RB	OCT4	(-)	Transcriptional	Rb was recruited to the *Oct4* promoter. Rb represses the OCT4 expression.	Kareta, M. S., Gorges, L. L., Sage, J., & Wernig, M. (2015). Inhibition of Pluripotency Networks by the Rb Tumor Suppressor Restricts Reprogramming and Article Inhibition of Pluripotency Networks by the Rb Tumor Suppressor Restricts Reprogramming and Tumorigenesis. 1–12. https://doi.org/10.1016/j.stem.2014.10.019
p53	OCT4	(-)	Transcriptional	p53 represses the OCT4 expression.	Li, M., He, Y., Dubois, W., Wu, X., Shi, J., & Huang, J. (2012). Article Distinct Regulatory Mechanisms and Functions for p53-Activated and p53-Repressed DNA Damage Response Genes in Embryonic Stem Cells. Molecular Cell, 46(1), 30–42. https://doi.org/10.1016/j.molcel.2012.01.020
NANOG	OCT4	(+)	Transcriptional	NANOG directly activates the *Oct4* expression.	Loh, Y. H., Wu, Q., Chew, J. L., Vega, V. B., Zhang, W., Chen, X., Bourque, G., George, J., Leong, B., Liu, J., Wong, K. Y., Sung, K. W., Lee, C. W., Zhao, X. D., Chiu, K. P., Lipovich, L., Kuznetsov, V. A., Robson, P., Stanton, L. W., Wei, C. L., … Ng, H. H. (2006). The Oct4 and Nanog transcription network regulates pluripotency in mouse embryonic stem cells. Nature genetics, 38(4), 431–440. https://doi.org/10.1038/ng1760
miR-34a	OCT4	(-)	Post-transcriptional	OCT4 is a target of miR-34a.	Ng, W. L., Chen, G., Wang, M., Wang, H., Story, M., Shay, J. W., Zhang, X., Wang, J., Amin, A. R., Hu, B., Cucinotta, F. A., & Wang, Y. (2014). OCT4 as a target of miR-34a stimulates p63 but inhibits p53 to promote human cell transformation. Cell Death & Disease, 5. https://doi.org/10.1038/cddis.2013.563
YAP1	OCT4	(+)	Transcriptional	YAP signaling activates the *Oct4* promoter.	Tamm, C., Böwer, N., & Annerén, C. (2011). Regulation of mouse embryonic stem cell self-renewal by a Yes-YAP-TEAD2 signaling pathway downstream of LIF. Journal of Cell Science, 124(7), 1136–1144. https://doi.org/10.1242/jcs.075796
GATA6	OCT4	(-)	Transcriptional	OCT4 expression is downregulated by GATA6 overexpression.	Wamaitha, S. E., del Valle, I., Cho, L. T. Y., Wei, Y., Fogarty, N. M. E., Blakeley, P., … Niakan, K. K. (2015). Gata6 potently initiates reprograming of pluripotent and differentiated cells to extraembryonic endoderm stem cells. Genes and Development, 29(12), 1239–1255. https://doi.org/10.1101/gad.257071.114

SNAI2	p16	(-)	Transcriptional	SNAI2 directly represses the p16 expression.	Zhu, P., Zhang, C., Gao, Y., Wu, F., Zhou, Y., & Wu, W. S. (2019). The transcription factor Slug represses p16Ink4a and regulates murine muscle stem cell aging. Nature Communications, 10(1). https://doi.org/10.1038/s41467-019-10479-4
FOXA2	p21	(+)	Transcriptional	FOXA2 activates *p21* promoter.	An, J. H., Jang, S. M., Kim, J. W., Kim, C. H., Song, P. I., & Choi, K. H. (2014). The expression of p21 is upregulated by forkhead box A1/2 in p53-null H1299 cells. FEBS Letters, 588(21), 4065–4070. https://doi.org/10.1016/j.febslet.2014.09.033
HNF4a	p21	(+)	Transcriptional	HNF4A is recruited to the *p21* promoter. HNF4A activate*s p21* promoter.	Chiba, H., Itoh, T., Satohisa, S., Sakai, N., Noguchi, H., Osanai, M., … Sawada, N. (2005). Activation of p21CIP1/WAF1 gene expression and inhibition of cell proliferation by overexpression of hepatocyte nuclear factor-4α. Experimental Cell Research, 302(1), 11–21. https://doi.org/10.1016/j.yexcr.2004.08.014Hwang-Verslues, W. W., & Sladek, F. M. (2008). Nuclear receptor hepatocyte nuclear factor 4α1 competes with oncoprotein c-Myc for control of the p21/WAF1 promoter. Molecular Endocrinology, 22(1), 78–90. https://doi.org/10.1210/me.2007-0298
c-Myc	p21	(-)	Transcriptional	*p21* promoter is repressed by c-Myc.	Claassen, G. F., & Hann, S. R. (2000). A role for transcriptional repression of p21CIP1 by c-Myc in overcoming transforming growth factor β-induced cell-cycle arrest. Proceedings of the National Academy of Sciences of the United States of America, 97(17), 9498–9503. https://doi.org/10.1073/pnas.150006697 Gartel, A. L., Ye, X., Goufman, E., Shianov, P., Hay, N., Najmabadi, F., & Tyner, A. L. (2001). Myc represses the p21^(WAF1/CIP1) promoter and interacts with Sp1/Sp3. Proceedings of the National Academy of Sciences, 98(8), 4510 LP – 4515. https://doi.org/10.1073/pnas.081074898
TGF-β1	p21	(+)	Transcriptional	*p21* promoter is activated by TGF-β1 signaling.	Datto, M. B., Li, Y., Panus, J. F., Howe, D. J., Xiong, Y., & Wang, X. F. (1995). Transforming growth factor β induces the cyclin-dependent kinase inhibitor p21 through a p53-independent mechanism. Proceedings of the National Academy of Sciences of the United States of America, 92(12), 5545–5549. https://doi.org/10.1073/pnas.92.12.5545 Ijichi, H., Otsuka, M., Tateishi, K., Ikenoue, T., Kawakami, T., Kanai, F., … Omata, M. (2004). Smad4-independent regulation of p21/WAF1 by transforming growth factor-β. Oncogene, 23(5), 1043–1051. https://doi.org/10.1038/sj.onc.1207222
SOX9	p21	(+)	Transcriptional	SOX9 activates *p21* promoter.	Panda, D. K., Miao, D., Lefebvre, V., Hendy, G. N., & Goltzman, D. (2001). The Transcription Factor SOX9 Regulates Cell Cycle and Differentiation Genes in Chondrocytic CFK2 Cells. Journal of Biological Chemistry, 276(44), 41229–41236. https://doi.org/10.1074/jbc.M104231200 Passeron, T., Valencia, J. C., Namiki, T., Vieira, W. D., Passeron, H., Miyamura, Y., & Hearing, V. J. (2009).

					Upregulation of SOX9 inhibits the growth of human and mouse melanomas and restores their sensitivity to retinoic acid. Journal of Clinical Investigation, 119(4), 954–963. https://doi.org/10.1172/JCI34015
NF-κB	p21	(+)	Transcriptional	NF-κB activates *p21* promoter.	Wuerzberger-Davis, S. M., Chang, P.-Y., Berchtold, C., & Miyamoto, S. (2005). Enhanced G2-M Arrest by Nuclear Factor-KB-Dependent p21waf1/cip1 Induction. Molecular Cancer Research, 3(6), 345 LP – 353. https://doi.org/10.1158/1541-7786.MCR-05-0028 Hellin, A.-C., Bentires-Alj, M., Verlaet, M., Benoit, V., Gielen, J., Bours, V., & Merville, M.-P. (2000). Roles of Nuclear Factor-κB, p53, and p21/WAF1 in Daunomycin-Induced Cell Cycle Arrest and Apoptosis. Journal of Pharmacology and Experimental Therapeutics, 295(3), 870 LP – 878. Retrieved from http://jpet.aspetjournals.org/content/295/3/870.abstract
β-catenin	p21	(-)	Transcriptional	p21 promoter activity is repressed by β-catenin signaling.	Xu, J., Chen, Y., Huo, D., Khramtsov, A., Khramtsova, G., Zhang, C., … Olopade, O. I. (2016). β-catenin regulates c-Myc and CDKN1A expression in breast cancer cells. Molecular Carcinogenesis, 55(5), 431–439. https://doi.org/10.1002/mc.22292 Kamei, J., Toyofuku, T., & Hori, M. (2003). Negative regulation of p21 by β-catenin/TCF signaling: A novel mechanism by which cell adhesion molecules regulate cell proliferation. Biochemical and Biophysical Research Communications, 312(2), 380–387. https://doi.org/10.1016/j.bbrc.2003.10.129
KLF4	p21	(+)	Transcriptional	KLF4 binds to the *p21* promoter. KLF4 activates p21 expression.	Zhang, W., Geiman, D. E., Shields, J. M., Dang, D. T., Mahatan, C. S., Kaestner, K. H., … Yang, V. W. (2000). The gut-enriched Kruppel-like factor (Kruppel-like factor 4) mediates the transactivating effect of p53 on the p21(WAF1)/(Cip)1 promoter. Journal of Biological Chemistry, 275(24), 18391–18398. https://doi.org/10.1074/jbc.C000062200 Sung, D. C., Chintharlapalli, S., Abdelrahim, M., Papineni, S., Liu, S., Guo, J., … Safe, S. (2008). 5,5′-Dibromo-bis(3′-indolyl)methane induces Krüppel-like factor 4 and p21 in colon cancer cells. Molecular Cancer Therapeutics, 7(7), 2109–2120. https://doi.org/10.1158/1535-7163.MCT-07-2311
p53	p21	(+)	Transcriptional	p53 regulates positively p21 expression.	Zhang, W., Geiman, D. E., Shields, J. M., Dang, D. T., Mahatan, C. S., Kaestner, K. H., … Yang, V. W. (2000). The gut-enriched Kruppel-like factor (Kruppel-like factor 4) mediates the transactivating effect of p53 on the p21(WAF1)/(Cip)1 promoter. Journal of Biological Chemistry, 275(24), 18391–18398. https://doi.org/10.1074/jbc.C000062200 Brugarolas, J., Chandrasekaran, C., Gordon, J. I., Beach, D., Jacks, T., & Hannon, G. J. (1995). Radiation-induced cell cycle arrest compromised by p21 deficiency. Nature, 377(6549), 552–557. https://doi.org/10.1038/377552a0

NF-κB	p53	(+)	Transcriptional	NF-κB direct binding activates the *p53* promotor.	Kirch, H. C., Flaswinkel, S., Rumpf, H., Brockmann, D., & Esche, H. (1999). Expression of human p53 requires synergistic activation of transcription from the p53 promoter by AP-1, NF-κB and Myc/Max. Oncogene, 18(17), 2728–2738. https://doi.org/10.1038/sj.onc.1202626 Hellin, A. C., Calmant, P., Gielen, J., Bours, V., & Merville, M. P. (1998). Nuclear factor - κB-dependent regulation of p53 gene expression induced by daunomycin genotoxic drug. Oncogene, 16(9), 1187–1195. https://doi.org/10.1038/sj.onc.1201638
OCT4	p53	(-)	Transcriptional	OCT4 represses the p53 expression.	Ng, W. L., Chen, G., Wang, M., Wang, H., Story, M., Shay, J. W., Zhang, X., Wang, J., Amin, A. R., Hu, B., Cucinotta, F. A., & Wang, Y. (2014). OCT4 as a target of miR-34a stimulates p63 but inhibits p53 to promote human cell transformation. Cell Death & Disease, 5. https://doi.org/10.1038/cddis.2013.563
p53	p53	(+)	Transcriptional	p53 binds to the *p53* promoter and activates its expression.	Wang, S., & El-deiry, W. S. (2006). p73 or p53 Directly Regulates Human p53 Transcription to Maintain Cell Cycle Checkpoints. 14, 6982–6990. https://doi.org/10.1158/0008-5472.CAN-06-0511
KLF4	p53	(+)	Transcriptional	KLF4 binds to the *p53* promoter.	Wassmann, S., Wassmann, K., Jung, A., Velten, M., Knuefermann, P., Petoumenos, V., Becher, U., Werner, C., Mueller, C., & Nickenig, G. (2007). Induction of p53 by GKLF is essential for inhibition of proliferation of vascular smooth muscle cells. Journal of Molecular and Cellular Cardiology, 43(3), 301–307. https://doi.org/10.1016/j.yjmcc.2007.06.001
HNF6	p53	(+)	Transcriptional	HNF6 is recruited to the *p53* promoter. HNF6 activates the *p53* promoter.	Yuan, X., Wang, D., Hu, Y., Tang, Y., Shi, W., Guo, X., & Song, J. (2013). Hepatocyte Nuclear Factor 6 Suppresses the Migration and Invasive Growth of Lung Cancer Cells through p53 and the Inhibition of Epithelial-Mesenchymal Transition *. 288(43), 31206–31216. https://doi.org/10.1074/jbc.M113.480285
SNAI2	SNAI1	(-)	Transcriptional	SNAI2 represses the SNAI1 promoter.	Chen, Y., & Gridley, T. (2013). Biochemical and Biophysical Research Communications The SNAI1 and SNAI2 proteins occupy their own and each other ' s promoter during chondrogenesis. Biochemical and Biophysical Research Communications, 435(3), 356–360. https://doi.org/10.1016/j.bbrc.2013.04.086 Nakamura, R., Ishii, H., Endo, K., Hotta, A., Fujii, E., Miyazawa, K., & Saitoh, M. (2018). Reciprocal expression of Slug and Snail in human oral cancer cells. PloS one, 13(7), e0199442. https://doi.org/10.1371/journal.pone.0199442
miR-34a	SNAI1	(-)	Post-transcriptional	SNAI1 is a target of mir-34a	Kim, N. H., Kim, H. S., Li, X., Lee, I., Choi, H., Kang, S. E., Cha, S. Y., Ryu, J. K., Yoon, D., Fearon, E. R., Rowe, R. G., Lee, S., Maher, C. A., Weiss, S. J., & Yook, J. I. (2011). A p53/miRNA-34 axis regulates Snail1-dependent cancer cell epithelial–mesenchymal transition. 195(3), 417–433. https://doi.org/10.1083/jcb.201103097 Siemens, H., Jackstadt, R., Hünten, S., Kaller, M., Menssen, A., Götz, U., & Hermeking, H. (2011). miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal

					transitions. Cell cycle (Georgetown, Tex.), 10(24), 4256–4271. https://doi.org/10.4161/cc.10.24.18552
GATA6	SNAI1	(-)	Transcriptional	GATA6 is recruited to the *SNAI1* promoter.	Martinelli, P., Carrillo-De Santa Pau, E., Cox, T., Sainz, B., Dusetti, N., Greenhalf, W., … Real, F. X. (2017). GATA6 regulates EMT and tumour dissemination, and is a marker of response to adjuvant chemotherapy in pancreatic cancer. Gut, 66(9), 1665–1676. https://doi.org/10.1136/gutjnl-2015-311256
YAP1	SNAI1	(+)	Transcriptional	YAP1 is recruited to the *Snai1* promoter. YAP signaling activates SNAI1 expression.	Noce, V., Battistelli, C., Cozzolino, A. M., Consalvi, V., Cicchini, C., Strippoli, R., … Amicone, L. (2019). YAP integrates the regulatory Snail/HNF4α circuitry controlling epithelial/hepatocyte differentiation. Cell Death and Disease, 10(10). https://doi.org/10.1038/s41419-019-2000-8
SNAI1	SNAI1	(-)	Transcriptional	SNAI1 represses its own promoter.	Peiró, S., Escrivà, M., Puig, I., Barberà, M. J., Dave, N., Herranz, N., Larriba, M. J., Takkunen, M., Francí, C., Muñoz, A., Virtanen, I., Baulida, J., & García de Herreros, A. (2006). Snail1 transcriptional repressor binds to its own promoter and controls its expression. Nucleic acids research, 34(7), 2077–2084. https://doi.org/10.1093/nar/gkl141
HNF1a	SNAI1	(-)	Transcriptional	HNF1a is recruited to the *Snai1* promoter. HNF1a overexpression downregulates SNAI1 expression.	Santangelo, L., Marchetti, A., Cicchini, C., Conigliaro, A., Conti, B., Mancone, C., … Tripodi, M. (2011). The stable repression of mesenchymal program is required for hepatocyte identity: A novel role for hepatocyte nuclear factor 4α. Hepatology, 53(6), 2063–2074. https://doi.org/10.1002/hep.24280
HNF4a	SNAI1	(-)	Transcriptional	HNF4a is recruited to the *Snai1* promoter. HNF4 expression is negatively correlated with SNAI1 expression.	Santangelo, L., Marchetti, A., Cicchini, C., Conigliaro, A., Conti, B., Mancone, C., … Tripodi, M. (2011). The stable repression of mesenchymal program is required for hepatocyte identity: A novel role for hepatocyte nuclear factor 4α. Hepatology, 53(6), 2063–2074. https://doi.org/10.1002/hep.24280
c-Myc	SNAI1	(+)	Transcriptional	c-Myc is recruited to the *SNAI1* promoter. c-Myc knockdown inhibits the TGF-β1-induced SNAI1 expression.	Smith, A., Verrecchia, A., Fagà, G. et al. A positive role for Myc in TGFβ-induced Snail transcription and epithelial-to-mesenchymal transition. Oncogene 28, 422–430 (2009). https://doi.org/10.1038/onc.2008.395
TGF-β1	SNAI1	(+)	Transcriptional	TGF-β1/SMAD signaling activates the *Snai1* promoter.	Thuault, S., Tan, E., Peinado, H., Cano, A., Heldin, C., & Moustakas, A. (2008). HMGA2 and Smads Co-regulate SNAIL1 Expression during Induction of Epithelial-to-Mesenchymal Transition * □. 283(48), 33437–33446. https://doi.org/10.1074/jbc.M802016200
OCT4	SNAI1	(+)	Transcriptional	OCT4 activates SNAI1 expression through STAT3 signaling.	Yin, X., Zhang, B., Zheng, S., Gao, D., Qiu, S., Wu, W., & Ren, Z. (2015). Coexpression of gene Oct4 and Nanog initiates stem cell characteristics in hepatocellular carcinoma and promotes epithelial-mesenchymal transition through activation of Stat3 / Snail signaling. 1–13.

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NANOG	SNAI1	(+)	Transcriptional	NANOG activates SNAI1 expression through STAT3 signaling.	Yin, X., Zhang, B., Zheng, S., Gao, D., Qiu, S., Wu, W., & Ren, Z. (2015). Coexpression of gene Oct4 and Nanog initiates stem cell characteristics in hepatocellular carcinoma and promotes epithelial-mesenchymal transition through activation of Stat3 / Snail signaling. 1–13. https://doi.org/10.1186/s13045-015-0119-3 Wang, D., Lu, P., Zhang, H., Luo, M., Zhang, X., Wei, X., & Gao, J. (2014). Oct-4 and Nanog promote the epithelial-mesenchymal transition of breast cancer stem cells and are associated with poor prognosis in breast cancer patients. 5(21).
SOX9	SNAI2	(+)	Transcriptional	SOX9 activates *SNAI2* promoter.	Daisuke, S., Suzuki, T., Osumi, N., & Wakamatsu, Y. (2006). Cooperative action of Sox9, Snail2 and PKA signaling in early neural crest development. Development, 133(7), 1323–1333. https://doi.org/10.1242/dev.02297 Lin, S. C., Chou, Y. T., Jiang, S. S., Chang, J. L., Chung, C. H., Kao, Y. R., … Wu, C. W. (2016). Epigenetic switch between SOX2 and SOX9 regulates cancer cell plasticity. Cancer Research, 76(23), 7036–7048. https://doi.org/10.1158/0008-5472.CAN-15-3178
YAP1	SNAI2	(+)	Transcriptional	YAP1 was recruited to the *SNAI2* promoter. YAP signaling activity correlates positively with SNAI2 expression.	Heallen, T., Zhang, M., Wang, J., Bonilla-Claudio, M., Klysik, E., Johnson, R. L., & Martin, J. F. (2011). Hippo Pathway Inhibits Wnt Signaling to Restrain Cardiomyocyte Proliferation and Heart Size. Science, 332(6028), 458 LP – 461. https://doi.org/10.1126/science.1199010 Yu, M., Chen, Y., Li, X., Yang, R., Zhang, L., Huangfu, L., … Shan, H. (2018). YAP1 contributes to NSCLC invasion and migration by promoting Slug transcription via the transcription co-factor TEAD. Cell Death and Disease, 9(5). https://doi.org/10.1038/s41419-018-0515-z
β-catenin	SNAI2	(+)	Transcriptional	β-catenin is recruited to the *Snai2* promoter. β-catenin signaling activates SNAI2 expression.	Lambertini, E., Franceschetti, T., Torreggiani, E., Penolazzi, L., Pastore, A., Pelucchi, S., … Piva, R. (2010). SLUG: A new target of lymphoid enhancer factor-1 in human osteoblasts. BMC Molecular Biology, 11, 1–12. https://doi.org/10.1186/1471-2199-11-13 Heallen, T., Zhang, M., Wang, J., Bonilla-Claudio, M., Klysik, E., Johnson, R. L., & Martin, J. F. (2011). Hippo Pathway Inhibits Wnt Signaling to Restrain Cardiomyocyte Proliferation and Heart Size. Science, 332(6028), 458 LP – 461. https://doi.org/10.1126/science.1199010
KLF4	SNAI2	(-)	Transcriptional	KLF4 is recruited to the *SNAI2* promoter. KLF4 represses SNAI2 expression.	Lin, Z. S., Chu, H. C., Yen, Y. C., Lewis, B. C., & Chen, Y. W. (2012). Krüppel-like factor 4, a tumor suppressor in hepatocellular carcinoma cells reverts epithelial mesenchymal transition by suppressing slug expression. PLoS ONE, 7(8). https://doi.org/10.1371/journal.pone.0043593 Liu, Y.-N., Abou-Kheir, W., Yin, J.

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miR-200a,b,c	SNAI2	(-)	Post-transcriptional	SNAI2 is a target of miR-200a,b,c.	Liu, Y., Yin, J. J., Hynes, P. G., Casey, O. M., Fang, L., Yi, M., Stephens, R. M., Seng, V., & Martin, P. (2013). MiR-1 and miR-200 inhibit EMT via Slug -dependent and tumorigenesis via Slug -independent mechanisms. January 2012, 296–306. https://doi.org/10.1038/onc.2012.58 Hoefert, J. E., Bjerke, G. A., Wang, D., & Yi, R. (2018). The microRNA-200 family coordinately regulates cell adhesion and proliferation in hair morphogenesis. 217(6), 2185–2204.
HNF1a	SNAI2	(-)	Transcriptional	HNF1a is recruited on the *SNAI2* promoter. HNF1a overexpression downregulates SNAI2 expression.	Santangelo, L., Marchetti, A., Cicchini, C., Conigliaro, A., Conti, B., Mancone, C., … Tripodi, M. (2011). The stable repression of mesenchymal program is required for hepatocyte identity: A novel role for hepatocyte nuclear factor 4α. Hepatology, 53(6), 2063–2074. https://doi.org/10.1002/hep.24280
HNF4A	SNAI2	(-)	Transcriptional	HNF4a is recruited to the *SNAI2* promoter. HNF1a overexpression downregulates SNAI2 expression.	Santangelo, L., Marchetti, A., Cicchini, C., Conigliaro, A., Conti, B., Mancone, C., … Tripodi, M. (2011). The stable repression of mesenchymal program is required for hepatocyte identity: A novel role for hepatocyte nuclear factor 4α. Hepatology, 53(6), 2063–2074. https://doi.org/10.1002/hep.24280
SNAI1	SNAI2	(-)	Transcriptional	SNAI1 represses the SNAI2 promoter activity.	Sundararajan, V., Tan, M., Tan, T. Z., Ye, J., & Thiery, J. P. (2019). SNAI1 recruits HDAC1 to suppress SNAI2 transcription during epithelial to mesenchymal transition. Scientific Reports, 1, 1–9. https://doi.org/10.1038/s41598-019-44826-8
FOXA2	SNAI2	(-)	Transcriptional	FOXA2 binds to the *SNAI2* promoter. FOXA2 represses SNAI2 expression.	Tang, Y., Shu, G., Yuan, X., Jing, N., & Song, J. (2011). FOXA2 functions as a suppressor of tumor metastasis by inhibition of epithelial-to-mesenchymal transition in human lung cancers. Cell Research, 21(2), 316–326. https://doi.org/10.1038/cr.2010.126
NANOG	SNAI2	(+)	Transcriptional	NANOG is recruited to the *SNAI2* promoter. NANOG activates the *SNAI2* promoter.	Yao, C., Su, L., Shan, J., Zhu, C., Liu, L., Liu, C., Xu, Y., Yang, Z., Bian, X., Shao, J., Li, J., Lai, M., Shen, J., & Qian, C. (2016). IGF/STAT3/NANOG/Slug Signaling Axis Simultaneously Controls Epithelial-Mesenchymal Transition and Stemness Maintenance in Colorectal Cancer. *Stem cells (Dayton, Ohio)*, *34*(4), 820–831. https://doi.org/10.1002/stem.2320
OCT4	SOX2	(+)	Transcriptional	OCT4 binds to the *SOX2* promoter. OCT4 knockdown decreases the *SOX2* promoter activity.	Chew, J. L., Loh, Y. H., Zhang, W., Chen, X., Tam, W. L., Yeap, L. S., Li, P., Ang, Y. S., Lim, B., Robson, P., & Ng, H. H. (2005). Reciprocal transcriptional regulation of Pou5f1 and Sox2 via the Oct4/Sox2 complex in embryonic stem cells.

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SOX2	SOX2	(+)	Transcriptional	SOX2 binds to the *SOX2* promoter. SOX2 knockdown decreases the SOX2 promoter activity.	Chew, J., Tam, W., Yeap, L., Li, P., Ang, Y., Lim, B., … Ng, H. (2005). Reciprocal Transcriptional Regulation of. Society, 25(14), 6031–6046. https://doi.org/10.1128/MCB.25.14.6031
miR-34a	SOX2	(-)	Post-transcriptional	SOX2 is a target of miR-34a.	Choi, Y. J., Lin, C., Ho, J. J., He, X., Okada, N., Bu, P., Zhong, Y., Kim, S. Y., Bennett, M. J., Chen, C., Ozturk, A., Hicks, G. G., Hannon, G. J., & He, L. (2011). miR-34 miRNAs provide a barrier for somatic cell reprogramming. Nature Cell Biology, 13(11). https://doi.org/10.1038/ncb2366
β-catenin	SOX2	(+)	Transcriptional	β-catenin is recruited to the *SOX2* promoter. β-catenin signaling activates SOX2 expression.	Heallen, T., Zhang, M., Wang, J., Bonilla-Claudio, M., Klysik, E., Johnson, R. L., & Martin, J. F. (2011). Hippo Pathway Inhibits Wnt Signaling to Restrain Cardiomyocyte Proliferation and Heart Size. Science, 332(6028), 458 LP – 461. https://doi.org/10.1126/science.1199010
YAP1	SOX2	(+)	Transcriptional	YAP1 is recruited to the *SOX2* promoter. YAP signaling activates SOX2 expression.	Heallen, T., Zhang, M., Wang, J., Bonilla-Claudio, M., Klysik, E., Johnson, R. L., & Martin, J. F. (2011). Hippo Pathway Inhibits Wnt Signaling to Restrain Cardiomyocyte Proliferation and Heart Size. Science, 332(6028), 458 LP – 461. https://doi.org/10.1126/science.1199010 Lian, I., Kim, J., Okazawa, H., Zhao, J., Zhao, B., Yu, J., … Guan, K. L. (2010). The role of YAP transcription coactivator in regulating stem cell self-renewal and differentiation. Genes and Development, 24(11), 1106–1118. https://doi.org/10.1101/gad.1903310
RB	SOX2	(-)	Transcriptional	Rb is recruited to the *Sox2* promoter and represses the SOX2 expression.	Kareta, M. S., Gorges, L. L., Sage, J., & Wernig, M. (2015). Inhibition of Pluripotency Networks by the Rb Tumor Suppressor Restricts Reprogramming and Article Inhibition of Pluripotency Networks by the Rb Tumor Suppressor Restricts Reprogramming and Tumorigenesis. 1–12. https://doi.org/10.1016/j.stem.2014.10.019 Vilas, J. M., Ferreirós, A., Carneiro, C., Morey, L., Da Silva-Álvarez, S., Fernandes, T., Abad, M., Di Croce, L., García-Caballero, T., Serrano, M., Rivas, C., Vidal, A., & Collado, M. (2015). Transcriptional regulation of Sox2 by the retinoblastoma family of pocket proteins. Oncotarget, 6(5), 2992–3002. https://doi.org/10.18632/oncotarget.2996
c-Myc	SOX2	(+)	Transcriptional	c-Myc is recruited to the *Sox2* promoter. c-Myc activates SOX2 expression.	Kwan, K. Y., Shen, J., & Corey, D. P. (2015). C-MYC transcriptionally amplifies SOX2 target genes to regulate self-renewal in multipotent otic progenitor cells. Stem Cell Reports, 4(1), 47–60. https://doi.org/10.1016/j.stemcr.2014.11.001 Lin, C. H., Lin, C. W., Tanaka, H., Fero, M. L., & Eisenman, R. N. (2009). Gene regulation and epigenetic remodeling in murine embryonic stem cells by c-Myc. PLoS ONE, 4(11). https://doi.org/10.1371/journal.pone.0007839

p53	SOX2	(-)	Transcriptional	p53 represses the *Sox2* expression.	Li, M., He, Y., Dubois, W., Wu, X., Shi, J., & Huang, J. (2012). Article Distinct Regulatory Mechanisms and Functions for p53-Activated and p53-Repressed DNA Damage Response Genes in Embryonic Stem Cells. Molecular Cell, 46(1), 30–42. https://doi.org/10.1016/j.molcel.2012.01.020
NANOG	SOX2	(+)	Transcriptional	NANOG activates the *Sox2* expression.	Loh, Y. H., Wu, Q., Chew, J. L., Vega, V. B., Zhang, W., Chen, X., Bourque, G., George, J., Leong, B., Liu, J., Wong, K. Y., Sung, K. W., Lee, C. W., Zhao, X. D., Chiu, K. P., Lipovich, L., Kuznetsov, V. A., Robson, P., Stanton, L. W., Wei, C. L., … Ng, H. H. (2006). The Oct4 and Nanog transcription network regulates pluripotency in mouse embryonic stem cells. Nature genetics, 38(4), 431–440. https://doi.org/10.1038/ng1760
miR-200c	SOX2	(-)	Post-transcriptional	SOX2 is a target of miR-200c.	Peng, C., Li, N., Ng, Y. K., Zhang, J., Meier, F., Theis, F. J., Merkenschlager, M., Chen, W., Wurst, W., & Prakash, N. (2012). A unilateral negative feedback loop between miR-200 microRNAs and Sox2/E2F3 controls neural progenitor cell-cycle exit and differentiation. Journal of Neuroscience, 32(38), 13292–13308. https://doi.org/10.1523/JNEUROSCI.2124-12.2012
p21	SOX2	(-)	Transcriptional	p21 is recruited to the *Sox2* enhancer. p21 represses the SOX2 expression.	Yamamizu, K., Schlessinger, D., & Ko, M. S. H. (2014). SOX9 accelerates ESC differentiation to three germ layer lineages by repressing SOX2 expression through P21 (WAF1/CIP1). Development (Cambridge), 141(22), 4254–4266. https://doi.org/10.1242/dev.115436 Marqués-Torrejón, M. Á., Porlan, E., Banito, A., Gómez-Ibarlucea, E., Lopez-Contreras, A. J., Fernández-Capetillo, Ó., … Fariñas, I. (2013). Cyclin-dependent kinase inhibitor p21 controls adult neural stem cell expansion by regulating Sox2 gene expression. Cell Stem Cell, 12(1), 88–100. https://doi.org/10.1016/j.stem.2012.12.001
FOXA2	SOX9	(+)	Transcriptional	FOXA2 knockdown decreases the *SOX9* expression.	Lee, K., Cho, H., Rickert, R. W., Li, Q. V., Pulecio, J., Leslie, C. S., & Huangfu, D. (2019). FOXA2 Is Required for Enhancer Priming during Pancreatic Differentiation. Cell Reports, 28(2), 382-393.e7. https://doi.org/10.1016/j.celrep.2019.06.034
SOX9	SOX9	(+)	Transcriptional	SOX9 activates its transcription.	Mead, T. J., Wang, Q., Bhattaram, P., Dy, P., Afelik, S., Jensen, J., & Lefebvre, V. (2013). A far-upstream (-70 kb) enhancer mediates Sox9 auto-regulation in somatic tissues during development and adult regeneration. Nucleic Acids Research, 41(8), 4459–4469. https://doi.org/10.1093/nar/gkt140
YAP1	SOX9	(+)	Transcriptional	*SOX9* promoter is activated by YAP signaling.	Song, S., Ajani, J. A., Honjo, S., Maru, D. M., Chen, Q., Scott, A. W., … Johnson, R. L. (2014). Hippo coactivator YAP1 upregulates SOX9 and endows esophageal Cancer cells with stem-like properties. Cancer Research, 74(15), 4170–4182. https://doi.org/10.1158/0008-5472.CAN-13-3569
NF-κB	SOX9	(+)	Transcriptional	NF-κB activates *SOX9* promoter.	Sun, L., Mathews, L. A., Cabarcas, S. M., Zhang, X., Yang, A., Zhang, Y., … Farrar, W. L. (2013). Epigenetic regulation of SOX9 by the NF-κB signaling pathway in pancreatic cancer stem cells. Stem Cells, 31(8), 1454–1466.

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c-Myc	SUZ12	(+)	Transcriptional	c-Myc is recruited to the *Suz12* promoter. SUZ12 expression decreases by c-Myc knockdown.	Krepelova, A., Neri, F., Maldotti, M., Rapelli, S., & Oliviero, S. (2014). Myc and Max genome-wide binding sites analysis links the Myc regulatory network with the polycomb and the core pluripotency networks in mouse embryonic stem cells. PLoS ONE, 9(2), 1–12. https://doi.org/10.1371/journal.pone.0088933 Neri, F., Zippo, A., Krepelova, A., Cherubini, A., Rocchigiani, M., & Oliviero, S. (2012). Myc Regulates the Transcription of the PRC2 Gene To Control the Expression of Developmental Genes in Embryonic Stem Cells. Molecular and Cellular Biology, 32(4), 840–851. https://doi.org/10.1128/mcb.06148-11
β-catenin	TELase	(+)	Transcriptional	*TERT* promoter is activated by β-catenin signaling.	Hoffmeyer, K., Raggioli, A., Rudloff, S., Anton, R., Hierholzer, A., Del Valle, I., … Kemler, R. (2012). Wnt/β-catenin signaling regulates telomerase in stem cells and cancer cells. Science, 336(6088), 1549–1554. https://doi.org/10.1126/science.1218370
KLF4	TELase	(+)	Transcriptional	KLF4 is recruited to the *TERT* promoter.	https://doi.org/10.18632/oncotarget.9141 Wong, C. W., Hou, P. S., Tseng, S. F., Chien, C. L., Wu, K. J., Chen, H. F., … Teng, S. C. (2010). Krüppel-like transcription factor 4 contributes to maintenance of telomerase activity in stem cells. Stem Cells, 28(9), 1510–1517. https://doi.org/10.1002/stem.477
TGF-β1	TELase	(-)	Transcriptional	TERT promoter activity is inhibited by TGF-β1 signaling through SMAD3 binding to the TERT promoter.	Li, H., Xu, D., Li, J., Berndt, M. C., & Liu, J. P. (2006). Transforming growth factor β suppresses human telomerase reverse transcriptase (hTERT) by Smad3 interactions with c-Myc and the hTERT gene. Journal of Biological Chemistry, 281(35), 25588–25600. https://doi.org/10.1074/jbc.M602381200 Lacerte, A., Korah, J., Roy, M., Yang, X. J., Lemay, S., & Lebrun, J. J. (2008). Transforming growth factor-β inhibits telomerase through SMAD3 and E2F transcription factors. Cellular Signalling, 20(1), 50–59. https://doi.org/10.1016/j.cellsig.2007.08.012
c-Myc	TELase	(+)	Transcriptional	c-Myc is recruited to the *TERT* promoter. c-Myc activates TERT expression.	Wang, J., Xie, L. Y., Allan, S., Beach, D., & Hannon, G. J. (1998). Myc activates telomerase. Genes and Development, 12(12), 1769–1774. https://doi.org/10.1101/gad.12.12.1769 Xu, D., Popov, N., Hou, M., Wang, Q., Björkholm, M., Gruber, A., … Henriksson, M. (2001). Switch from Myc/Max to Mad1/Max binding and decrease in histone acetylation at the telomerase reverse transcriptase promoter during differentiation of HL60 cells. Proceedings of the National Academy of Sciences of the United States of America, 98(7), 3826–3831. https://doi.org/10.1073/pnas.071043198

E2F1	TELase	(+)	Transcriptional	E2F1 was recruited to the *TERT* promoter. E2F1 activates the TERT promoter in the absence of Rb.	Won, J., Chang, S., Oh, S., & Kim, T. K. (2004). Small-molecule-based identification of dynamic assembly of E2F-pocket protein-histone deacetylase complex for telomerase regulation in human cells. Proceedings of the National Academy of Sciences of the United States of America, 101(31), 11328–11333. https://doi.org/10.1073/pnas.0401801101 Crowe, D. L., & Nguyen, D. C. (2001). Rb and E2F-1 regulate telomerase activity in human cancer cells. Biochimica et Biophysica Acta - Gene Structure and Expression, 1518(1–2), 1–6. https://doi.org/10.1016/S0167-4781(00)00296-7
RB	TELase	(-)	Transcriptional	Rb is recruited to the *TERT* promoter. Rb inhibits the *TERT* promoter activity.	Won, J., Chang, S., Oh, S., & Kim, T. K. (2004). Small-molecule-based identification of dynamic assembly of E2F-pocket protein-histone deacetylase complex for telomerase regulation in human cells. Proceedings of the National Academy of Sciences of the United States of America, 101(31), 11328–11333. https://doi.org/10.1073/pnas.0401801101 Beitzinger, M., Oswald, C., Beinoraviciute-Kellner, R., & Stiewe, T. (2006). Regulation of telomerase activity by the p53 family member p73. Oncogene, 25(6), 813–826. https://doi.org/10.1038/sj.onc.1209125
p53	TELase	(-)	Transcriptional	*TERT* promoter is repressed by p53.	Xu, D., Wang, Q., Gruber, A., Björkholm, M., Chen, Z., Zaid, A., … Pisa, P. (2000). Downregulation of telomerase reverse transcriptase mRNA expression by wild type p53 in human tumor cells. Oncogene, 19(45), 5123–5133. https://doi.org/10.1038/sj.onc.1203890 Kanaya, T., Kyo, S., Hamada, K., Takakura, M., Kitagawa, Y., Harada, H., & Inoue, M. (2000). Adenoviral expression of p53 represses telomerase activity through down- regulation of human telomerase reverse transcriptase transcription. Clinical Cancer Research, 6(4), 1239–1247.
SNAI1	TELase	(-)	Transcriptional	SNAI1 is recruited to the *TERT* promoter. *TERT* promoter activity is inhibited by SNAI1 overexpression.	Yoo, Y. S., Park, S., Gwak, J., Ju, B. G., & Oh, S. (2015). Involvement of transcription repressor Snail in the regulation of human telomerase reverse transcriptase (hTERT) by transforming growth factor-β. Biochemical and Biophysical Research Communications, 465(1), 131–136. https://doi.org/10.1016/j.bbrc.2015.07.146
ZEB1	TELase	(+)	Transcriptional	ZEB1 is recruited to the *TERT* promoter. ZEB1 activates *TERT* promoter.	Yu, P., Shen, X., Yang, W., Zhang, Y., Liu, C., & Huang, T. (2018). ZEB1 stimulates breast cancer growth by up-regulating hTERT expression. Biochemical and Biophysical Research Communications, 495(4), 2505–2511. https://doi.org/10.1016/j.bbrc.2017.12.139
YAP1	TELase	(+)	Transcriptional	*TERT* promoter is activated by YAP signaling.	Zhang, Q., Liu, N., Bai, J., Zhou, Q., Mao, J., Xu, L., … Cong, Y. S. (2020). Human telomerase reverse transcriptase is a novel target of Hippo-YAP pathway. FASEB Journal, 34(3), 4178–4188. https://doi.org/10.1096/fj.201902147R
GATA6	TGF-β1	(-)	Transcriptional	GATA6 represses the TGF-β1 transcription.	Froese, N., Kattih, B., Breitbart, A., Grund, A., Geffers, R., Molkentin, J. D., Kispert, A., Wollert, K. C., Drexler, H., & Heineke, J. (2011). GATA6 promotes

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YAP1	TGF-β1	(+)	Indirect transcriptional	YAP/TAZ activates the TGF-β1 signaling.	Qin, Z., Xia, W., Fisher, G. J., Voorhees, J. J., & Quan, T. (2018). YAP/TAZ regulates TGF-β/Smad3 signaling by induction of Smad7 via AP-1 in human skin dermal fibroblasts. Cell Communication and Signaling : CCS, 16(1), 18. https://doi.org/10.1186/s12964-018-0232-3 Lee, D. H., Park, J. O., Kim, T. S., Kim, S. K., Kim, T. H., Kim, M. C., Park, G. S., Kim, J. H., Kuninaka, S., Olson, E. N., Saya, H., Kim, S. Y., Lee, H., & Lim, D. S. (2016). LATS-YAP/TAZ controls lineage specification by regulating TGFβ signaling and Hnf4α expression during liver development. Nature Communications, 7(May). https://doi.org/10.1038/ncomms11961
KLF4	TGF-β1	(-)	Indirect transcriptional	KLF4 downregulates the TGF-β1 signaling.	Sun, H., Peng, Z., Tang, H., Xie, D., Jia, Z., Zhong, L., Zhao, S., Ma, Z., Gao, Y., Zeng, L., Luo, R., & Xie, K. (2017). Loss of KLF4 and consequential downregulation of Smad7 exacerbate oncogenic TGF-β signaling in and promote progression of hepatocellular carcinoma. Oncogene, 36(21), 2957–2968. https://doi.org/10.1038/onc.2016.447
FOXA2	TNFa	(-)	Transcriptional	FOXA2 knockout induces TNFa expression.	Bochkis, I. M., Schug, J., Rubins, N. E., Chopra, A. R., O'Malley, B. W., & Kaestner, K. H. (2009). Foxa2-dependent hepatic gene regulatory networks depend on physiological state. Physiological genomics, 38(2), 186–195. https://doi.org/10.1152/physiolgenomics.90376.2008
TWIST1	TNFa	(-)	Transcriptional	TWIST1 represses the TNFa expression.	Šošić, D., Richardson, J. A., Yu, K., Ornitz, D. M., & Olson, E. N. (2003). Twist regulates cytokine gene expression through a negative feedback loop that represses NF-kappaB activity. Cell, 112(2), 169–180. https://doi.org/10.1016/s0092-8674(03)00002-3
mirR-34a	TWIST1	(-)	Post-transcriptional	TWIST1 is a target of miR-34a	Imani, S., Wei, C., Cheng, J., Khan, M. A., Fu, S., Yang, L., Tania, M., Zhang, X., Xiao, X., Zhang, X., & Fu, J. (2017). MicroRNA-34a targets epithelial to mesenchymal transition-inducing transcription factors (EMT-TFs) and inhibits breast cancer cell migration and invasion. Oncotarget, 8(13), 21362–21379. https://doi.org/10.18632/oncotarget.15214
β-catenin	YAP1	(+)	Transcriptional	Wnt/β-catenin signaling activates YAP1 expression and transcriptional activity.	Konsavage, W. M., Kyler, S. L., Rennoll, S. A., Jin, G., & Yochum, G. S. (2012). Wnt/β-catenin signaling regulates yes-associated protein (YAP) gene expression in colorectal carcinoma cells. Journal of Biological Chemistry, 287(15), 11730–11739. https://doi.org/10.1074/jbc.M111.327767 Azzolin, L., Panciera, T., Soligo, S., Enzo, E., Bicciato, S., Dupont, S., Bresolin, S., Frasson, C., Basso, G., Guzzardo, V., Fassina, A., Cordenonsi, M., & Piccolo, S. (2014). YAP/TAZ incorporation in the β-catenin destruction complex orchestrates the

					Wnt response. Cell, 158(1), 157–170. https://doi.org/10.1016/j.cell.2014.06.013
p53	YAP1	(-)	Indirect transcriptional	p53 negatively regulates *Yap1.*	Mello, S. S., Valente, L. J., Raj, N., Hruban, R. H., Curtis, C., & Attardi, L. D. (2017). Article A p53 Super-tumor Suppressor Reveals a Tumor Suppressive p53-Ptpn14-Yap Axis in Pancreatic Article A p53 Super-tumor Suppressor Reveals a Tumor Suppressive p53-Ptpn14-Yap Axis in Pancreatic Cancer. Cancer Cell, 32(4), 460-473.e6. https://doi.org/10.1016/j.ccell.2017.09.007 Furth, N., Aylon, Y., & Oren, M. (2018). p53 shades of Hippo. Cell death and differentiation, 25(1), 81–92. https://doi.org/10.1038/cdd.2017.163
HNF4a	YAP1	(-)	Transcriptional	HNF4A is recruited to the *Yap1* promoter. HNF4A represses YAP1 expression.	Noce, V., Battistelli, C., Cozzolino, A. M., Consalvi, V., Cicchini, C., Strippoli, R., … Amicone, L. (2019). YAP integrates the regulatory Snail/HNF4α circuitry controlling epithelial/hepatocyte differentiation. Cell Death and Disease, 10(10). https://doi.org/10.1038/s41419-019-2000-8 Cai, W. Y., Lin, L. Y., Hao, H., Zhang, S. M., Ma, F., Hong, X. X., … Li, B. A. (2017). Yes-associated protein/TEA domain family member and hepatocyte nuclear factor 4-alpha (HNF4α) repress reciprocally to regulate hepatocarcinogenesis in rats and mice. Hepatology, 65(4), 1206–1221. https://doi.org/10.1002/hep.28911
SOX2	YAP1	(+)	Transcriptional	SOX2 regulates YAP1 at the transcriptional level.	Seo, E., Basu-Roy, U., Gunaratne, P. H., Coarfa, C., Lim, D. S., Basilico, C., & Mansukhani, A. (2013). SOX2 regulates YAP1 to maintain stemness and determine cell fate in the osteo-adipo lineage. Cell reports, 3(6), 2075–2087. https://doi.org/10.1016/j.celrep.2013.05.029
TWIST1	ZEB1	(+)	Transcriptional	TWIST1 is recruited to the *ZEB1* promoter. TWIST1 stimulates ZEB1 expression.	Dave, N., Guaita-Esteruelas, S., Gutarra, S., Frias, À., Beltran, M., Peiró, S., & García De Herreros, A. (2011). Functional cooperation between snail1 and twist in the regulation of ZEB1 expression during epithelial to mesenchymal transition. Journal of Biological Chemistry, 286(14), 12024–12032. https://doi.org/10.1074/jbc.M110.168625
miR-200a,b	ZEB1	(-)	Post-transcriptional	ZEB1 is a target of miR-200a,b.	Gregory, P. A., Bert, A. G., Paterson, E. L., Barry, S. C., Tsykin, A., Farshid, G., Vadas, M. A., Khew-Goodall, Y., & Goodall, G. J. (2008). The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nature Cell Biology, 10(5), 593–601. https://doi.org/10.1038/ncb1722
mirR-34a	ZEB1	(-)	Post-transcriptional	ZEB1 is a target of miR-34a.	Imani, S., Wei, C., Cheng, J., Khan, M. A., Fu, S., Yang, L., Tania, M., Zhang, X., Xiao, X., Zhang, X., & Fu, J. (2017). MicroRNA-34a targets epithelial to mesenchymal transition-inducing transcription factors (EMT-TFs) and inhibits breast cancer cell migration and invasion. Oncotarget, 8(13), 21362–21379. https://doi.org/10.18632/oncotarget.15214
HNF1A	ZEB1	(-)	Indirect transcriptional	HNF1A activates the miR-192 expression. ZEB1 is a target of miR-192.	Jenkins, R. H., Martin, J., Phillips, A. O., Bowen, T., & Fraser, D. J. (2012). Transforming growth factor β1 represses proximal tubular cell microRNA-192

					expression through decreased hepatocyte nuclear factor DNA binding. Biochemical Journal, 443(2), 407–416. https://doi.org/10.1042/BJ20111861
GATA6	ZEB1	(-)	Transcriptional	GATA6 is recruited to the *ZEB1* promoter.	Martinelli, P., Carrillo-De Santa Pau, E., Cox, T., Sainz, B., Dusetti, N., Greenhalf, W., … Real, F. X. (2017). GATA6 regulates EMT and tumour dissemination, and is a marker of response to adjuvant chemotherapy in pancreatic cancer. Gut, 66(9), 1665–1676. https://doi.org/10.1136/gutjnl-2015-311256
β-catenin	ZEB1	(+)	Transcriptional	*ZEB1* promoter is activated by β-catenin signaling.	Sánchez-Tilló, E., De Barrios, O., Siles, L., Cuatrecasas, M., Castells, A., & Postigo, A. (2011). β-catenin/TCF4 complex induces the epithelial-to-mesenchymal transition (EMT)-activator ZEB1 to regulate tumor invasiveness. Proceedings of the National Academy of Sciences of the United States of America, 108(48), 19204–19209. https://doi.org/10.1073/pnas.1108977108
SNAI2	ZEB1	(+)	Transcriptional	SNAI2 is recruited to the *ZEB1* promoter.SNAI2 overexpression activates the *ZEB1* promoter.	Wels, C., Joshi, S., Koefinger, P., Bergler, H., & Schaider, H. (2011). Transcriptional activation of ZEB1 by slug leads to cooperative regulation of the epithelial-mesenchymal transition-like phenotype in melanoma. Journal of Investigative Dermatology, 131(9), 1877–1885. https://doi.org/10.1038/jid.2011.142
FOXC2	ZEB1	(+)	Transcriptional	FOXC2 activates ZEB1 expression.	Werden, S. J., Sphyris, N., Sarkar, T. R., Paranjape, A. N., Labaff, A. M., Taube, J. H., Hollier, B. G., Ramirez-peña, E. Q., & Soundararajan, R. (2016). Phosphorylation of serine 367 of FOXC2 by p38 regulates ZEB1 and breast cancer metastasis , without impacting primary tumor growth. Nature Publishing Group, 35(46), 5977–5988. https://doi.org/10.1038/onc.2016.203
miR-200c	ZEB1	(-)	Post-transcriptional	ZEB1 is a target of miR-200c.	Zhou, X., Wang, Y., Shan, B., Han, J., Zhu, H., Lv, Y., Fan, X., Sang, M., Liu, X. De, & Liu, W. (2015). The downregulation of miR-200c/141 promotes ZEB1/2 expression and gastric cancer progression. Medical Oncology, 32(1), 1–13. https://doi.org/10.1007/s12032-014-0428-3
EZH2	β-catenin	(+)	Indirect transcriptional	EZH2 activates the wnt-β-catenin signaling through GSK-3β repression.	Chen, Q., Zheng, P. S., & Yang, W. T. (2016). EZH2-mediated repression of GSK-3β and TP53 promotes Wnt/β-catenin signaling-dependent cell expansion in cervical carcinoma. Oncotarget, 7(24), 36115–36129. https://doi.org/10.18632/oncotarget.8741
BMI1	β-catenin	(+)	Indirect transcriptional	BMI1 activates the wnt/β-catenin signaling through DKK1 repression.	Cho, J. H., Dimri, M., & Dimri, G. P. (2013). A positive feedback loop regulates the expression of polycomb group protein BMI1 via WNT signaling pathway. Journal of Biological Chemistry, 288(5), 3406–3418. https://doi.org/10.1074/jbc.M112.422931
TGF-β1	β-catenin	(+)	Prot-prot interaction	TGF-β1 activates the β-catenin signaling through SMAD3-β-catenin interaction.	Li, T. F., Chen, D., Wu, Q., Chen, M., Sheu, T. J., Schwarz, E. M., Drissi, H., Zuscik, M., & O'Keefe, R. J. (2006). Transforming growth factor-β stimulates cyclin D1 expression through activation of β-catenin signaling in chondrocytes. Journal of Biological Chemistry, 281(30), 21296–21304. https://doi.org/10.1074/jbc.M600514200

p53	β-catenin	(-)	Transcriptional	p53 downregulates to β-catenin.	Sadot, E., Geiger, B., Oren, M., & Ev, A. B. (2001). Down-Regulation of B -Catenin by Activated p53. 21(20), 6768–6781. https://doi.org/10.1128/MCB.21.20.6768
SOX2	β-catenin	(-)	Indirect transcriptional	Sox2 downregulates the β-catenin signaling.	Seo, E., Basu-Roy, U., Zavadil, J., Basilico, C., & Mansukhani, A. (2011). Distinct Functions of Sox2 Control Self-Renewal and Differentiation in the Osteoblast Lineage. Molecular and Cellular Biology, 31(22), 4593–4608. https://doi.org/10.1128/mcb.05798-11
miR-200a	β-catenin	(-)	Post-transcriptional	β-catenin is a target of miR-200a.	Su, J., Zhang, A., Shi, Z., Ma, F., Pu, P., Wang, T. A. O., Zhang, J. I. E., Kang, C., & Zhang, Q. (2012). MicroRNA-200a suppresses the Wnt / β -catenin signaling pathway by interacting with β -catenin. 1162–1170. https://doi.org/10.3892/ijo.2011.1322