

SUPPLEMENTAL DATA

**SOX11 MODULATES REDOX HOMEOSTASIS AND CHEMORESISTANCE
VIA TCL1A AND PRDX2 UPREGULATION IN AGGRESSIVE MCL**

Patricia Balsas^{1,2†}, Anna De Bolòs^{1*}, Marta Sureda-Gómez^{1*}, Maria Carreras-Caballé,
Marta-Leonor Rodríguez¹, Elias Campo^{1,2,3}, Virginia Amador^{1,2†},

SUPPLEMENTARY TABLES**Table S1. List of primers used for RT-PCR**

Gene	Primers
PRDX1	Forward: 5'-CCCTCTTGACTTCACCTTTGT-3'
	Reverse: 5'-TCCACAGAAGCACCAATCAC-3'
PRDX2	Forward: 5'-CAACGTGGATGACAGCAAGG-3'
	Reverse: 5'-AGGGCGTCACTATTCAGCTT-3'
PRDX3	Forward: 5'-GTAACATCTTGGTGGCTGGC-3'
	Reverse: 5'-AGGACCGTTGATCAGAAGCT-3'
PRDX5	Forward: 5'-CGGGTATGGGACTAGCTGG-3'
	Reverse: 5'-GGCTCTGCTGAAACTGCG-3'
PRDX6	Forward: 5'-GTCCTTCCAACCATCCCTGA-3'
	Reverse: 5'-AACACAATTGGCAGCTGACA-3'
TCL1A	Forward: 5'-TTAGCACTACCACTCCTGCC-3'
	Reverse: 5'-TCTCACAAGTTCACGGAGCT-3'
VEGFA	Forward: 5'-CTACCTCCACCATGCCAAGTG-3'
	Reverse: 5'-TGCGCTGATAGACATCCATGA-3'

PDK1	Forward: 5'-GAAGCAGTTCCTGGACTTCG-3'
	Reverse: 5'-ACCAATTGAACGGATGGTGT-3'
GUSB	Forward: 5'-CGTGGTTGGAGAGCTCATT-3'
	Reverse: 5'-GAACGCTGCACTTTTGGTT-3'

Table S2. Gene Ontology annotations for molecular functions using the 83 significant DEG in SOX11+ vs SOX11- MCLs in the two MCL primary series (GSE79196) and (EGAD00010001842)) . Only GO terms with Benjamini values <0.05 are shown.

GO term	p-value	Benjamini
Peroxidase activity	4.3E-14	1.6E-11
Glutathione peroxidase activity	3.9E-12	7.3E-10
Peroxiredoxin activity	1.2E-8	1.1E-6
Thioredoxin peroxidase activity	1.2E-8	1.1E-6
Identical protein binding	3.4E-5	2.5E-3
Antioxidant activity	7.5E-5	4.7E-3
Glutathione transferase activity	2.2E-4	1.2E-2
Enzyme binding	2.2E-4	1.2E-2
Protein binding	6.5E-4	2.7E-2
RNA polymerase II sequence-specific DNA binding transcription factor binding	1.2E-3	4.4E-2
Protein homodimerization activity	1.3E-3	4.4E-2
Protein C-terminus binding	1.5E-3	4.8E-2

Table S3. Correlation between the expression of SOX11 in GSE79196, EGAD00010001842 and GSE93291 MCL series and the 83 oxidative stress- and antioxidant-related genes commonly enriched in SOX11+ compared to SOX11-MCL samples in GEPs of GSE79196 and EGAD00010001842 series. R Pearson coefficient and p-value are indicated in the table. Genes with p-value<0.001 in common in the three series are in bold.

	GSE79196		EGAD00010001842		GSE93291	
Gene	R Pearson	P-value	R Pearson	P-value	R Pearson	P-value
PXDN	0.57476	5.48E-8	0.68071	1.85E-7	0.19806	0.02875
GSTP1	0.68534	1.08E-6	0.68139	1.79E-8	-0.05429	0.55257
HBB	0.30459	0.0251	-0.07425	0.6532	-0.18278	0.04390
TP53INP1	0.13503	0.3303	0.15579	0.3436	-0.16401	0.07105
PRDX5	0.35100	0.0093	0.35862	0.0250	-0.11124	0.22254
TXNRD1	0.56030	1.05E-9	0.54317	0.0004	0.00165	0.98561
S100A9	0.15580	0.2606	-0.03440	0.8353	-0.27486	0.00218
MGST2	0.60113	1.54E-8	0.68495	1.51E-7	-0.02403	0.79278
TXNDC17	0.46540	0.0004	0.55906	0.0002	-0.18715	0.03901

PRDX1	0.39252	0.0033	0.48201	0.0019	0.08776	0.33646
PRDX3	0.31344	0.0210	0.41117	0.0093	-0.00254	0.97786
MGST1	0.16002	0.2477	0.25984	0.1102	-0.31357	0.00044
GPX7	0.22610	0.1002	0.33549	0.0368	-0.18082	0.04625
PTGS2	0.09925	0.4752	0.07758	0.6387	-0.17506	0.05377
GPX1	0.24505	0.0741	0.42576	0.0069	-0.27277	0.00237
CLIC2	0.37145	0.0057	0.49076	0.0015	-0.23026	0.01073
ALOX5AP	0.08838	0.5251	0.38961	0.0142	0.12943	0.15535
PRDX6	0.45065	0.0006	0.55083	0.0003	0.03805	0.67736
PRDX2	0.50108	0.0001	0.53658	0.0004	0.29999	0.00079
DHFR	0.29467	0.0305	0.32680	0.0423	-0.20387	0.02430
CD36	0.13585	0.3274	0.31038	0.0545	-0.34287	0.00011
FBLN5	0.32365	0.0170	0.55265	0.0003	0.08097	0.37529
ATP7A	0.20209	0.1428	0.56672	0.0002	0.12176	0.18156
PON2	0.86817	0.0019	0.82752	8.24E-3	0.29965	0.00080

PTPRK	0.36985	0.0059	0.11109	0.5008	-0.17368	0.05573
PKD2	0.66392	4.43E-6	0.65110	7.17E-8	0.17489	0.05402
NET1	0.44421	0.0008	0.58105	0.0001	0.20736	0.02192
CD38	0.56894	7.16E-8	0.65526	5.98E-8	0.34477	0.00010
MSRB2	0.62079	5.5E-7	0.65030	7.42E-8	0.13782	0.13008
APOD	0.37739	0.0049	0.40157	0.0113	0.02501	0.78451
DAPK1	0.33798	0.0124	0.45959	0.0032	-0.02585	0.77747
STAU2	0.45328	0.0006	0.53165	0.0005	0.21682	0.01645
ECT2	0.50016	0.0001	0.39742	0.0122	-0.29284	0.00106
PCNA	0.39088	0.0035	0.37323	0.0193	-0.28475	0.00148
CDK1	0.41111	0.0020	-0.38401	0.0158	-0.31530	0.00040
MELK	0.40846	0.0022	0.32052	0.0467	-0.14866	0.10223
TLR4	0.60173	1.49E-8	0.65675	5.6E-8	0.01221	0.89381
PAWR	0.48685	0.0002	0.36918	0.0207	0.36681	3.24E-9
EZH2	0.39720	0.0029	0.35374	0.0272	-0.03372	0.71233

MYEF2	0.20918	0.1290	0.29589	0.0674	0.27922	0.00184
ABL1	0.64431	1.46E-7	0.54223	0.0004	0.53324	2.56E-4
FOS	0.11240	0.4184	0.14462	0.3797	-0.09878	0.27903
PXN	0.47153	0.0003	0.67774	2.14E-8	0.26245	0.00350
SIRPA	0.36708	0.0063	0.73063	1.28E-7	0.17974	0.04759
ATOX1	0.39101	0.0035	0.55256	0.0003	-0.26959	0.00267
TBC1D24	0.37567	0.0051	0.35267	0.0277	0.28574	0.00142
NCOA7	0.32172	0.0177	0.47429	0.0023	0.11989	0.18839
TRPM2	0.55455	1.35E-9	0.50241	0.0011	0.04096	0.65422
STX2	0.27105	0.0474	0.29390	0.0694	-0.04312	0.63719
CASP3	0.27604	0.0433	0.47355	0.0023	-0.00644	0.94390
PPP2CB	0.45920	0.0005	0.72352	1.95E-7	0.28297	0.00159
HDAC2	0.40044	0.0027	0.33200	0.0389	-0.12237	0.17935
CHD6	0.47629	0.0003	0.20037	0.2213	0.13202	0.14719
AKR1C3	0.40729	0.0022	0.22018	0.1780	-0.07031	0.44155

NUDT1	0.28809	0.0346	0.49345	0.0014	0.13218	0.14668
IDH1	0.38574	0.0040	0.59712	5.99E-6	0.20413	0.02412
ALOX5	0.49689	0.0001	0.58256	9.97E-9	0.48068	2.1E-6
NDUFB4	0.26185	0.0558	0.49019	0.0015	0.30016	0.00078
PDCD10	0.47233	0.0003	0.33701	0.0359	-0.21797	0.01587
STAT1	0.20485	0.1373	0.36762	0.0213	-0.04320	0.63658
HSPB1	0.26701	0.0510	0.24577	0.1315	0.13916	0.12634
ALS2	0.43850	0.0009	0.30710	0.0572	0.07868	0.38901
ETV5	0.03560	0.7983	0.38486	0.0156	-0.23846	0.00817
KEAP1	0.31673	0.0196	0.36178	0.0236	-0.12555	0.16821
ANXA1	0.03949	0.7768	0.38204	0.0164	-0.08756	0.33754
C19orf12	0.21841	0.1126	0.33158	0.0392	0.24303	0.00699
BNIP3	0.24395	0.0755	0.44760	0.0043	0.07418	0.41678
RBX1	0.47266	0.0003	0.44740	0.0043	-0.14196	0.11882
ROMO1	0.27737	0.0423	0.56133	0.0002	-0.17122	0.05933

MCTP1	0.32083	0.0180	0.33088	0.0396	-0.18322	0.04338
AIF1	0.13007	0.3485	0.52965	0.0005	-0.22169	0.01413
HYAL2	0.41990	0.0016	0.48589	0.0017	-0.26038	0.00377
IMPACT	0.08578	0.5374	0.42547	0.0069	-0.29238	0.00108
MAPK8	0.16603	0.2302	0.28545	0.0782	0.22725	0.01183
ADAM9	0.02053	0.8829	0.28226	0.0817	-0.19814	0.02869
RBM11	0.27977	0.0405	0.07222	0.6622	-0.08997	0.32434
VKORC1L1	0.23504	0.0871	0.51996	0.0007	-0.18969	0.03638
SMPD3	0.25271	0.0652	0.43542	0.0056	0.16846	0.06362
PSMB5	0.31767	0.0192	0.51804	0.0007	0.11509	0.20681
CTNNB1	0.22164	0.1072	0.37637	0.0182	0.15978	0.07875
ERCC8	0.30364	0.0256	0.43482	0.0057	-0.09769	0.28443
APEX1	0.36581	0.0065	0.58990	7.744E-9	0.25438	0.00469
NDUFA12	0.23903	0.0817	0.28094	0.0832	-0.33401	0.00017

Table S4. Prognostic impact of the 4 oxidative stress- and antioxidant-related genes commonly upregulated in SOX11+ compared to SOX11- MCL samples in GSE79196 and EGAD00010001842 series and with positive correlation with SOX11 expression (p-value < 0.001). Survival analysis done using previously published GEP and clinical data from GSE79196 MCL series. Hazard ratios (HR), and p-value are indicated in the table.

GSE79196		
Gene	HR	P-value
PRDX2	5.27	0.0015
CD38	2.489	1e-04
ABL1	5.496	0.004
ALOX5	2.411	0.142

Table S5. Bivariate Cox regression analysis used to evaluate the independent prognosis value of PRDX2, CD38 and ABL1 mRNA expression (continuous) in presence of other high-risk factors (categorical; SOX11 status, copy number alterations (CNA), *TP53* alterations, *CDKN2A* alterations and MCL proliferation signature) in GSE79196 MCL primary series.

	HR	95% CI	P-value
PRDX2 mRNA expression	4.2	[1.5-12]	0.007
SOX11 status	3.7	[1.1-12]	0.037
PRDX2 mRNA expression	4.9	[1.85-13.2]	0.001
CNA (≤ 6 vs > 6)	1.9	[0.72-4.9]	0.196
PRDX2 mRNA expression	5	[1.72-14.4]	0.003
17p/<i>TP53</i>alterations	1.2	[0.75-4.9]	0.177
PRDX2 mRNA expression	4.2	[1.46-12]	0.008
9p/<i>CDKN2A</i>alterations	3.4	[0.83-14]	0.09
PRDX2 mRNA expression	3.9	[1.4-11]	0.009
MCL proliferation signature	4.3	[1.5-12]	0.006
CD38 mRNA expression	2.2	[1.32-3.5]	0.002
SOX11 status	3.2	[0.95-10.9]	0.061
CD38 mRNA expression	2.14	[1.3-3.6]	0.005
CNA (≤ 6 vs > 6)	0.87	[0.3-2.5]	0.788
CD38 mRNA expression	2	[1.25-3.3]	0.004
17p/<i>TP53</i>alterations	2	[0.78-5.2]	0.148
CD38 mRNA expression	1.9	[1.1-3.2]	0.021
9p/<i>CDKN2A</i>alterations	3.8	[0.88-16.6]	0.073

CD38 mRNA expression	2.1	[1.3-3.3]	0.001
MCL proliferation signature	4.9	[1.7-13.8]	0.003
ABL1 mRNA expression	2.6	[0.63-11]	0.184
SOX11 status	3	[0.75-12]	0.12
ABL1 mRNA expression	5.4	[1.09-26.5]	0.039
CNA (≤ 6 vs > 6)	1.3	[0.36-4.8]	0.686
ABL1 mRNA expression	3.6	[1.05-12.2]	0.041
17p/TP53alterations	1.9	[0.73-4.8]	0.192
ABL1 mRNA expression	3.1	[0.94-10]	0.064
9p/CDKN2Aalterations	5.5	[1.34-23]	0.018
ABL1 mRNA expression	6.3	[1.8-23]	0.005
MCL proliferation signature	5.7	[2.1-16]	<0.001

Table S6. Differentially expressed genes in PRDX2-high and -low expressing MCL cases (GSE79196). Log₂ transformed fold change (Log FC) and adjusted p-value are indicated in the table. Only genes with an absolute Log FC ≥ 2 and adjusted p value (adj p value) ≤ 0.05 were considered.

MCL primary samples series GSE79196		
Gene	Log FC	Adj p value
PRDX2	2.92616482	8.99E-13
NREP	2.71346435	0.00596119
PCDH9	2.65819158	0.00670271
HDGFL3	2.29852232	0.02643344
TCL1A	2.24645088	0.02002541
DPYSL2	2.22204914	0.00210525
HBB	2.11361305	0.03867532
CDCA7	2.10305188	0.00732655
IGLC1	2.0783413	0.03329368
CHL1	2.06772761	0.0181119
FHL1	2.05879671	0.00522347
SLAMF7	-2.12180135	0.00344277

Table S7. Bivariate Cox regression models used to evaluate the independent prognosis value of TCL1A mRNA expression (continuous) in presence of other MCL high risk factors (categorical; SOX11 status, copy number alterations (CNA), TP53 alterations, CDKN2a alterations and MCL proliferation signature) estimated with MCL primary samples series EGAD00010001842.

	HR	95% CI	P-value
TCL1A mRNA expression	1.42	[1.1-15.7]	0.037
SOX11 status	0.02	[0.2-4.4]	0.975
TCL1A mRNA expression	1.26	[1.1-11.7]	0.04
CNA (≤ 6 vs > 6)	0.51	[0.6-5]	0.358
TCL1A mRNA expression	1.29	[1.1-11.7]	0.031
17p/TP53alterations	1.06	[0.9-8.4]	0.053
TCL1A mRNA expression	1.37	[1.1-13.7]	0.031
9p/CDKN2Aalterations	0.16	[0.3-4.1]	0.802
TCL1A mRNA expression	1.69	[1.4-20.6]	0.013
MCL proliferation signature	-0.45	[0.2-2.1]	0.454

SUPPLEMENTARY FIGURES

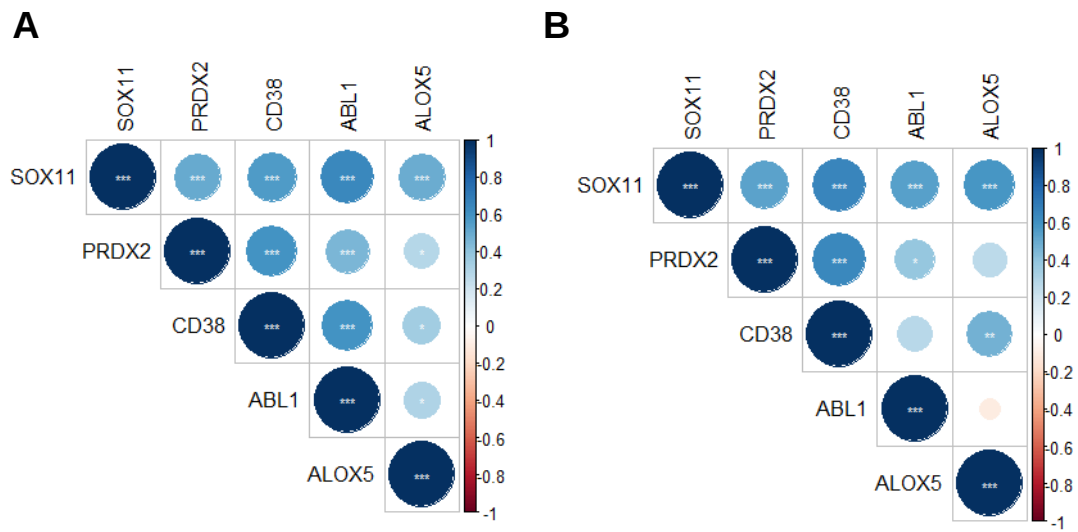
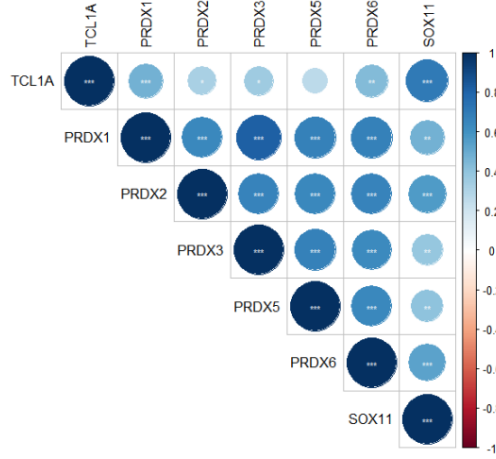
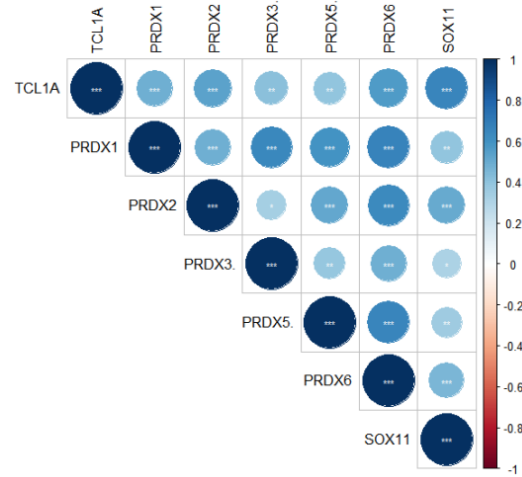


Figure S1. SOX11 correlates with PRDX2 expression in MCL. (A-B) Correlation of SOX11 with PRDX2, CD38, ANL1 and ALOX5 mRNA levels in **(A)** 30 SOX11+ and 24 SOX11- MCL primary cases, using GSE79196 dataset; and **(B)** 27 SOX11+ and 12 SOX11- MCL primary cases, using EGAD00010001842 dataset. Blue and red color indicates positive and negative correlation, respectively. Pearson statistical signification is indicated for each gene correlation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

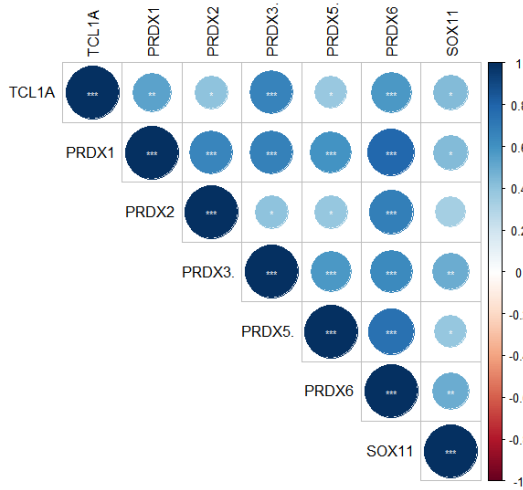
A



B



C



D

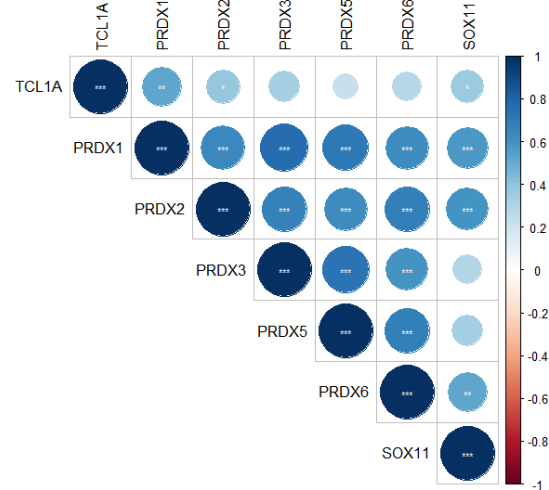


Figure S2. TCL1A correlates with PRDXs and SOX11 expression in MCL. (A-B)

Correlation of TCL1A with PRDXs and SOX11 mRNA levels in **(A)** 30 SOX11+ and 24 SOX11- MCL primary cases, using GSE79196 dataset; and **(B)** 27 SOX11+ and 12 SOX11- MCL primary cases, using EGAD00010001842 dataset. **(C-D)** Correlation of TCL1A with PRDXs and SOX11 mRNA levels in **(C)** SOX11+ MCL primary cases

(GSE79196 dataset) and **(D)** (EGAD00010001842 dataset). Blue and red color indicates positive and negative correlation, respectively. Pearson statistical signification is indicated for each gene correlation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The significance of difference was determined by independent samples Student t test: * $p < 0.05$, *** $p < 0.001$.

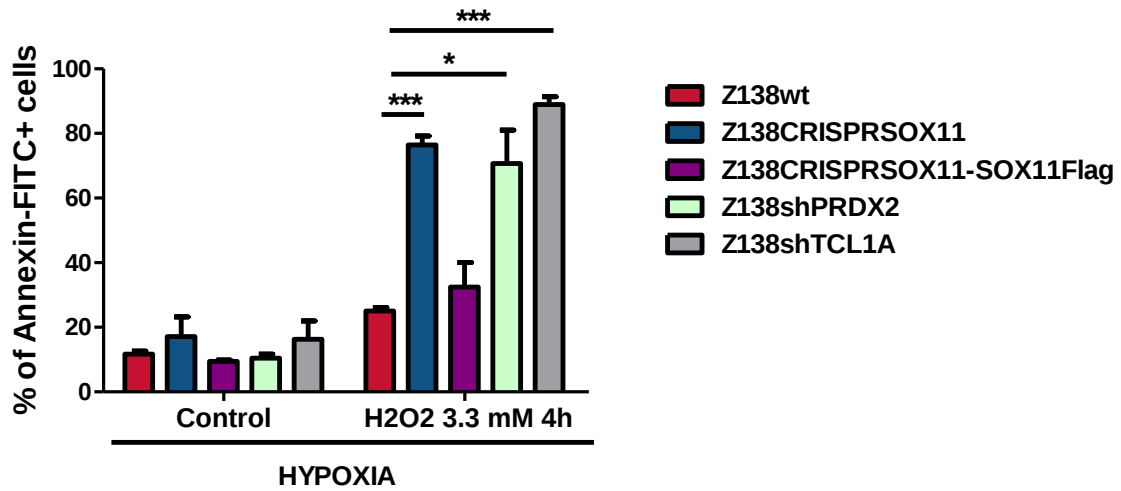


Figure S3. SOX11, TCL1A and PRDX2 protect MCL cells from oxidative stress. % of Annexin-FITC+ cells in Z138WT, Z138SOX11KO, Z138SOX11KO-SOX11Flag, Z138PRDX2KD and Z138TCL1AKD MCL cell lines after treated with 3.3 mM hydrogen peroxide (H₂O₂) for 4h in culture under hypoxia conditions (1.2%O₂ 24h). The significance of difference was determined by independent samples Student t test: *p<0.05, ***p<0.001.