

Supplementary Table 1. Protein expression (pg/mL) values of cytokines in isolated exosomes.

Exosomes were purified by ultracentrifugation of conditioned media derived from A549 cells treated with 3-MA (20 mM, 24 h), or Wortmannin (10 µM, 24 h). NPX values were measured by NGS (Next Generation Sequencing) using O-link cytokines panels. (p-value: Kruskal-Wallis)

Uniprot ID	ClindID	Unit	LLOQ	ULOQ	Status	ctrl1	ctrl2	ctrl3	ctrl4	Wort1	Wort2	Wort3	Wort4	Wort5	3-MA1	3-MA2	3-MA3	3-MA4	3-MA5	Aver. Control	Aver. Secretory autophagy inhibitors	p-value (Kruskal-Wallis)	secretory autophagy substrates	leader sequence	type	
CCL8	P80075	OID0558	pg/mL	0.02980	1953.12500	Pass	0.02738	0.01849	0.03359	0.04246	0.01403	0.01259	0.01756	0.00538	0.00540	0.01791	0.01945	0.01928	0.01856	0.01639	0.03048	0.01466	0.016	o	o	Chemokine
IL33	O95760	OID0558	pg/mL	0.21111	7875.82160	Fail																				
CCL12	I48061	OID0558	pg/mL	54.74972	31249.99966	Fail																				
OLN1	P78380	OID0558	pg/mL	0.95367	3906.25002	Pass	0.96132	0.96272	1.23891	2.0163	0.90071	0.9284	0.81249	0.45748	0.22618	0.96803	1.03688	1.07591	0.90474	0.75394	1.29865	0.80648	0.048	o	x	Other
IL27	Q8NEV9	OID0558	pg/mL	0.46561	31460.11545	Pass	0.12783	0.12636	0.11429	No Data	0.11296	0.15638	0.11022	0.12149	0.13202	0.23645	0.21418	No Data	No Data	No Data	0.12283	0.15353	0.569	x	o	Interleukin
IL2	P60568	OID0558	pg/mL	0.08701	2462.12763	Pass	0.00488	0.00479	0.00405	No Data	0.00403	0.00660	0.00380	0.00449	0.00513	0.01081	0.01007	0.00529	0.00514	No Data	0.00467	0.00615	0.309	x	o	Interleukin
CXCL9	Q07325	OID0558	pg/mL	0.20358	2591.12024	Fail																				
TGFA	P01135	OID0558	pg/mL	1.09252	1953.12499	Fail																				
IL1B	P01584	OID0558	pg/mL	0.35141	9092.61111	Pass	0.01488	0.01564	0.16321	0.15251	No Data	0.00495	No Data	No Data	0.01288	0.0055	No Data	0.00520	0.0052	0.0051	0.01564	0.00713	0.008	o	x	Interleukin
IL6	P05231	OID0558	pg/mL	0.25261	3906.25000	Pass	1.92095	No Data	2.90973	3.82071	1.85540	1.80818	No Data	1.66454	1.66191	No Data	No Data	1.58390	1.64474	1.77182	2.88380	1.71293	0.017	o	x	Interleukin
IL4	P05112	OID0559	pg/mL	0.04032	2708.23365	Fail																				
TNFSF12	O43508	OID0559	pg/mL	3.81470	15625.00004	Pass	2.57034	2.41947	3.16511	4.87375	6.40750	6.41197	2.93694	2.22628	2.06635	6.89321	5.90809	4.30827	3.65226	3.12279	3.25717	4.39337	0.396	x	x	TNFSF
TSPL	Q96909	OID0559	pg/mL	0.35825	6502.63051	Pass	0.37851	0.09191	0.08621	0.18468	0.04976	0.05601	0.03429	0.03961	0.04458	0.08847	0.09396	0.04581	0.08195	0.04889	0.18533	0.05833	0.016	o	x	Other
CCL11	P51671	OID0559	pg/mL	0.47467	21120.40567	Fail																				
HGF	P14210	OID0559	pg/mL	0.22239	15624.80340	Pass	1.22723	1.05842	3.16085	2.81635	2.64770	2.34574	1.16391	1.20859	1.05856	1.77558	2.04568	1.42663	1.31271	1.39539	2.06571	1.62805	0.671	x	o	Growthfactor
FLT3LG	I48771	OID0559	pg/mL	0.95367	3906.25003	Pass	0.00921	No Data	No Data	0.00617	0.05205	No Data	No Data	0.02558	0.01851	0.02766	0.03947	No Data	No Data	0.01780	0.00769	0.03018	0.046	x	o	Other
IL17E	Q36904	OID0559	pg/mL	0.29683	2778.81533	Fail																				
IL7	P13232	OID0559	pg/mL	0.26528	1663.86574	Pass	0.03742	0.01401	0.03832	No Data	0.02086	0.07014	No Data	0.01930	0.00993	0.06582	0.00544	0.05631	0.03320	0.02752	0.02992	0.03428	0.926	x	o	Interleukin
IL13	P35225	OID0560	pg/mL	0.49957	5589.85042	Pass	1.93677	1.92239	1.80288	1.86258	No Data	No Data	1.87440	1.97765	No Data	2.73892	2.00311	1.98007	2.06623	1.88116	2.10673	0.033	x	o	Interleukin	
IL18	Q14116	OID0560	pg/mL	0.46128	15461.77307	Pass	0.62036	0.70079	0.69750	0.68344	0.49638	0.63721	0.48363	0.52183	0.55709	No Data	No Data	0.56580	0.55791	0.58746	0.67552	0.55091	0.011	o	x	Interleukin
CCL13	Q99616	OID0560	pg/mL	0.05960	1953.12500	Fail																				
TNFSF10	P50591	OID0560	pg/mL	1.68650	7549.62677	Pass	No Data	0.62036	0.05631	0.11292	0.00513	No Data	0.02597	0.00461	0.04678	No Data	0.06817	0.01822	0.00424	No Data	0.08462	0.02473	0.03	o	x	TNFSF
CXCL10	P02778	OID0560	pg/mL	0.44190	3255.69720	Fail																				
IFNG	P01579	OID0560	pg/mL	0.03993	3881.80300	Pass	0.00250	No Data	No Data	No Data	No Data	No Data	0.00117	No Data	No Data	No Data	0.00695	No Data	0.00275	No Data	0.00250	0.00364	0.655	x	o	Interferone
IL10	P22301	OID0560	pg/mL	1.32012	40348.01106	Fail																				
CCL19	Q99731	OID0560	pg/mL	0.95367	976.56250	Pass	0.05222	0.04815	0.03849	0.04390	0.09753	0.05134	0.03725	0.04070	0.04393	0.07240	0.06873	0.08721	0.04400	0.04672	0.04569	0.05898	0.396	x	o	Chemokine
TNFB	P01375	OID0560	pg/mL	3.81470	15625.00004	Pass	0.32954	No Data	0.40352	0.82841	0.02518	0.10038	No Data	0.38558	0.36922	0.29907	No Data	0.08866	0.01343	0.04788	0.52049	0.16618	0.041	o	x	TNFSF
IL15	I48933	OID0561	pg/mL	0.77529	36391.17531	Pass	No Data	0.25909	0.25485	0.45369	No Data	0.12117	0.24466	0.02739	0.05551	0.16548	0.15181	0.02911	0.27013	0.06512	0.32254	0.12560	0.033	o	x	Interleukin
CCL3	P10147	OID0561	pg/mL	0.05109	1364.45024	Fail																				
CCL8	P10145	OID0561	pg/mL	0.30225	2908.32512	Pass	90.99438	82.32681	187.75888	264.15172	68.30817	67.43872	95.00884	51.35865	49.55825	101.47506	88.09600	80.86808	74.21840	81.49178	156.30795	75.78220	0.034	o	o	Chemokine
MMP12	P39900	OID0561	pg/mL	7.62939	15624.99990	Pass	0.11570	0.11204	0.08277	0.09194	0.08200	0.05780	0.18124	0.10005	0.13625	0.39361	0.35651	0.13294	0.12688	0.14986	0.10191	0.22221	0.048	x	o	Other
CSF2	P04141	OID0561	pg/mL	0.28971	5648.64588	Pass	0.38260	0.31517	0.46519	0.54313	0.34044	0.26970	0.29662	0.14960	0.16085	0.28124	0.23565	0.26043	0.24082	0.28794	0.42652	0.25233	0.007	o	o	Colony stimulating factor
CSF3	P09919	OID0561	pg/mL	10.37567	45131.79122	Pass	3.80983	3.52057	4.34469	8.47125	4.27381	2.67531	No Data	1.75928	1.90289	3.16214	4.14503	4.15192	3.08052	2.66443	5.28659	3.09059	0.064	o	o	Colony stimulating factor
VEGFA	P15692	OID0561	pg/mL	0.47684	7812.50003	Pass	65.43305	67.85739	91.00097	128.35981	82.08436	72.59656	72.23773	50.84125	47.58167	98.09971	81.69865	76.54121	68.48920	73.26443	88.16281	72.34348	0.671	x	x	Growthfactor
IL17C	Q36904	OID0561	pg/mL	0.73021	7812.50041	Fail																				
EGF	P01133	OID0561	pg/mL	0.47684	976.56250	Fail																				
CCL2	P13500	OID0561	pg/mL	0.23842	3906.25002	Pass	358.01123	353.70532	377.17322	588.50604	315.42675	312.58779	285.18331	207.74807	195.68810	No Data	No Data	305.03743	282.89302	349.50082	421.84895	281.75816	0.07	o	o	Chemokine
IL17A	Q16552	OID0562	pg/mL	0.22831	16668.32578	Pass	0.15007	0.14806	0.13158	0.13977	0.13113	0.18920	0.12602	0.14140	0.15580	No Data	0.26865	0.15939	No Data	0.16836	0.14237	0.16749	0.308	x	o	Interleukin
OSM	P13725	OID0562	pg/mL	0.13071	1761.96226	Pass	0.00446	0.00433	0.00324	0.00379	0.00321	0.00690	0.00585	0.00390	0.00482	0.01279	0.01176	0.00505	0.00484	0.00561	0.00396	0.00647	0.048	x	o	Other
CSF1	P06603	OID0562	pg/mL	0.14814	2622.48569	Pass	3.25938	3.44946	6.95824	8.43734	5.12238	4.41115	4.12465	2.97475	3.03216	6.27343	5.63336	4.64762	3.26000	3.50070	5.52611	4.29802	0.48	x	o	Colony stimulating factor
CCL4	P13236	OID0562	pg/mL	0.11921	3906.25001	Pass	0.02693	0.03099	0.04970	0.05036	0.03218	No Data	No Data	No Data	No Data	0.01003	No Data	No Data	0.00919	0.02645	0.03275	0.01987	0.327	x	o	Chemokine
CCL11	Q14625	OID0562	pg/mL	0.11921	1953.12499	Fail																				
LTA	P01374	OID0562	pg/mL	0.95135	1557.29331	Fail																				
CCL7	P80098	OID0562	pg/mL	0.11921	1953.12500	Pass	0.02123	0.02097	0.02706	0.02102	0.01882	0.02615	0.01817	0.02013	0.02195	0.03812	0.03603	0.04371	0.05342	0.02731	0.02257	0.03038	0.396	x	o	Chemokine
MMP1	P03956	OID0562	pg/mL	3.55673	9816.36280	Pass	25.32805	26.03384	33.74470	50.93831	25.05944	23.37537	24.62860	16.25838	15.97567	40.82633	36.35184	24.11888	21.75956	21.47435	34.01123	24.98484	0.048	o	x	Other

Supplementary Table 2. Immunoblotting intensity of intracellular and extracellular cytokine fractions.

Exosomes were isolated by PEG-based isolation of conditioned media derived from A549 cells treated with 3-MA (20 mM, 24 h), or Wortmannin (10 μ M, 24 h). (n=3)

		Wortmannin					3-MA				
		Average	Stddev	S.E.	Heatmap	Inhibition type	Average	Stddev	S.E.	Heatmap	Inhibition type
IL-1 β	cell	2.279757	0.304829	0.215546		secretion	1.728749	0.785461	0.555405		secretion
	exo	0.314046	0.162772	0.115097			0.637457	0.030161	0.021327		
IL18	cell	2.052677	0.464459	0.328422		secretion	1.050508	0.359868	0.254465		secretion
	exo	0.308808	0.021597	0.015271			0.260804	0.075361	0.053288		
HMGB1	cell	3.15614	0.968122	0.684565		secretion	2.987602	0.627983	0.444051		secretion
	exo	0.969744	0.228361	0.131844			0.744332	0.021473	0.015184		
ANXA2	cell	1.284589	0.847734	0.599438		secretion	0.739449	0.04766	0.0337		expression secretion
	exo	0.693375	0.062058	0.043882			0.596043	0.148285	0.104853		
TNF α	cell	0.949295	0.095183	0.067305		expression secretion	1.274011	0.110042	0.077811		secretion
	exo	0.314046	0.042106	0.029773			0.637457	0.07557	0.053436		
TGF β	cell	0.299235	0.070072	0.049548		expression secretion	0.729919	0.072414	0.051205		expression secretion
	exo	0.813515	0.003508	0.002481			0.855153	0.044219	0.031268		
IL-6	cell	1.750868	0.98531	0.568869		secretion	0.634014	0.246682	0.142422		expression secretion
	exo	0.488364	0.107733	0.0622			0.490831	0.343736	0.198456		
IL-15	cell	1.253269	0.339093	0.239775		secretion	0.766048	0.102211	0.072274		expression secretion
	exo	0.536354	0.013847	0.009791			0.6706	0.399371	0.282398		
IL-32	cell	1.394918	0.211669	0.149673		secretion	0.467793	0.294986	0.208587		expression secretion
	exo	0.64309	0.030693	0.021703			0.239927	0.046374	0.032792		
IL-33	cell	2.748006	0.794181	0.561571		secretion	1.447899	0.633824	0.448181		secretion
	exo	0.913828	1.511073	1.06849			0.414281	0.382127	0.270204		
IL-37	cell	0.888069	0.02632	0.018611		expression secretion	1.172318	0.14491	0.102467		expression secretion
	exo	0.708618	0.084605	0.059825			0.791459	0.111141	0.078589		
IL-12 β	cell	3.911026	1.987461	1.405347		secretion	6.599091	2.175793	1.538518		secretion
	exo	0.817953	0.041337	0.02923			0.632796	0.339218	0.239863		
IL-14	cell	1.162908	0.04981	0.035221		secretion	1.201027	0.134815	0.095329		secretion
	exo	0.991827	0.007249	0.005126			0.89727	0.08007	0.056618		
IFNL3	cell	0.815118	0.123431	0.087279		expression secretion	0.719858	0.008282	0.005856		expression secretion
	exo	0.927843	0.256338	0.181258			0.5914	0.287603	0.203366		
MIF	cell	0.982169	0.170353	0.120458		expression secretion	1.727211	0.176467	0.124781		secretion
	exo	0.398803	0.070149	0.049603			0.592158	0.021989	0.015548		
AIMP1	cell	1.815398	0.625111	0.360908		secretion	2.179922	2.008169	1.159417		secretion
	exo	1.006547	0.424857	0.245291			0.354652	0.174505	0.100751		
CTF1	cell	2.958713	0.326621	0.230956		secretion	2.157733	0.676602	0.47843		secretion
	exo	0.992033	0.12603	0.089117			0.949176	0.153459	0.108512		
THNSL2	cell	1.544774	0.223096	0.157753		secretion	2.278772	0.421124	0.29778		secretion
	exo	0.836623	0.193888	0.1371			0.744963	0.265304	0.187598		
VSTM1	cell	0.630874	0.194881	0.137801		expression secretion	0.908149	0.164944	0.116633		expression secretion
	exo	0.842091	0.07612	0.053825			0.947563	0.06728	0.047574		

Supplementary Table 3. Immunoblotting intensity of intracellular and extracellular cytokine fractions.

Exosomes were isolated by PEG-based isolation of conditioned media derived from A549 cells treated with oxidative stress (CoCl₂ (250 µM, 24 h)), ER stress (MG132 (0.5 µM, 24 h), Thapsigargin (TG; 200 nM, 24 h)), autophagy inhibition (Hydroxychloroquine (HCQ; 25 µM, 24 h)), or Starvation (Serum-free media, 6 h). (n=3)

		Oxidative stress					ER stress					Autophagy inhibition					Starvation				
		Average	Stdev	S.E.	Heatmap	Regulation type	Average	Stdev	S.E.	Heatmap	Regulation type	Average	Stdev	S.E.	Heatmap	Regulation type	Average	Stdev	S.E.	Heatmap	Regulation type
IL-12p	cell	5.590961	2.284426	1.318914		expression	0.955029	0.422438	0.243894		expression	1.817034	0.050985	0.029436		secretion	2.963868	0.11714952	0.067636307		secretion
	exo	11.34824	1.557151	0.899022		secretion	0.5082	0.156559	0.09039		secretion	0.913008	0.257346	0.148579		secretion	0.629975	0.11714952	0.067636307		secretion
IL-32	cell	88.31271	20.14592	11.63125		expression	1.836015	1.577686	0.910879		expression	0.707203	0.039949	0.020755		secretion	0.405922	0.11714952	0.067636307		expression
	exo	9.628127	2.243791	1.295453		secretion	2.191503	0.97063	0.580394		secretion	1.040782	0.067721	0.039099		secretion	0.426305	0.341065333	0.196914162		secretion
IL-6	cell	3.312596	3.373321	1.947598		expression	0.885975	0.365046	0.210761		expression	1.483354	0.377096	0.217716		secretion	1.744408	1.05695076	0.610230806		secretion
	exo	3.815037	1.680652	0.970325		secretion	0.511063	0.148269	0.085603		secretion	0.731389	0.146701	0.084698		secretion	0.385946	0.295268647	0.170473433		secretion
IL-16	cell	0.577594	0.019559	0.011292		secretion	1.124834	0.856103	0.494271		expression	9.559941	10.78234	6.225185		expression	2.109047	0.093904308	0.054215677		secretion
	exo	3.741191	1.472368	0.850072		secretion	1.441975	0.098473	0.056853		secretion	8.67656	6.412297	3.702142		secretion	0.819311	0.052181666	0.030127099		secretion
AIMP1	cell	1.27591	0.044551	0.256662		expression	2.900212	3.147896	1.817439		expression	0.51878	0.039805	0.022981		secretion	0.689201	0.146961081	0.08484802		secretion
	exo	1.811378	0.571152	0.329755		secretion	3.425597	2.906961	1.678335		secretion	3.333838	0.303599	0.175283		secretion	1.005568	1.013785666	0.585309427		secretion
CTF1	cell	0.581247	0.042344	0.029942		secretion	1.274475	0.748113	0.528996		secretion	0.844873	0.065346	0.046206		secretion	0.669312	0.782857848	0.553564093		secretion
	exo	1.702456	1.477259	1.04456		secretion	0.702316	0.140937	0.099658		secretion	7.866306	0.877979	0.620825		secretion	3.396255	3.638058045	2.784627548		secretion
HMG1	cell	1.846315	0.41068	0.290394		expression	1.230124	0.070496	0.049848		expression	1.379191	0.075485	0.053376		expression	0.486411	0.055872162	0.039507584		expression
	exo	1.664898	0.544726	0.38518		secretion	4.943784	2.09934	1.484458		secretion	1.119976	0.097656	0.069053		secretion	0.129526	0.082333067	0.05821827		secretion
IL-18	cell	7.290885	8.67388	6.133359		expression	0.764778	0.110487	0.078126		expression	1.089142	0.502323	0.355196		expression	1.657701	2.238487252	1.582849515		secretion
	exo	1.366781	0.44448	0.314295		secretion	0.648617	0.057218	0.040459		secretion	1.074812	0.372445	0.263359		secretion	0.559794	0.591638921	0.418351893		secretion
IFNL3	cell	0.979143	0.04662	0.032966		secretion	0.504816	0.028068	0.019847		expression	0.601421	0.10188	0.07204		expression	0.793614	0.03976165	0.028115732		expression
	exo	1.136961	0.305891	0.216298		secretion	0.163165	0.164941	0.116631		secretion	0.22303	0.279536	0.197662		secretion	0.451169	0.136497122	0.096518041		secretion
IL-33	cell	1.773412	0.501766	0.354802		expression	0.257146	0.003781	0.002673		secretion	1.201613	0.036535	0.025834		secretion	0.611783	0.076817188	0.054317955		expression
	exo	1.062029	0.069294	0.06314		secretion	1.137564	0.131392	0.092608		secretion	0.627009	0.04068	0.028906		secretion	0.049911	0.061276916	0.043329524		secretion
IL-37	cell	1.353027	0.158883	0.112346		secretion	1.638981	0.116847	0.082694		expression	1.122334	0.044558	0.031507		secretion	10.83112	10.5038139	7.425244442		secretion
	exo	0.847608	0.554107	0.391813		expression	46.78835	3.866301	2.506608		secretion	85.67943	8.589072	6.073392		secretion	0.130921	0.000838036	0.000592581		secretion
MIF	cell	0.195115	0.025738	0.0182		expression	9.402459	1.228744	0.868853		expression	8.791965	6.575504	5.649584		expression	0	0	0		N/A
	exo	0.873062	0.222177	0.157103		secretion	11.30758	1.639868	1.159562		secretion	1.772458	0.230827	0.163219		secretion	0	0	0		N/A
ANXA2	cell	1.027673	0.094227	0.066629		secretion	3.651891	0.041571	0.029395		expression	1.238269	0.043288	0.030609		secretion	1.431948	1.356244258	0.959009512		secretion
	exo	0.846204	0.025969	0.018377		secretion	1.927951	0.288441	0.203959		secretion	0.783398	0.008089	0.005072		secretion	0.659967	0.013169377	0.009312156		secretion
IL-14	cell	0.913232	0.031857	0.022527		expression	0.411758	0.072392	0.051189		secretion	0.75126	0.352504	0.249258		secretion	0.588451	0.016130374	0.011405897		secretion
	exo	0.768543	0.969253	0.685365		secretion	3.469359	1.420654	1.004554		secretion	2.558836	0.630566	0.445877		secretion	1.019351	0.735736842	0.52024451		secretion
IL-1β	cell	3.513837	1.575821	1.114274		secretion	1.71887	2.095222	1.481546		expression	1.071462	0.067796	0.047939		expression	4.978803	0.231916348	0.163989622		secretion
	exo	0.668661	0.116255	0.082204		secretion	1.979539	1.366931	0.966566		secretion	1.555291	0.009274	0.006558		secretion	0.093833	0.07813529	0.055249993		secretion
VSTM1	cell	1.650963	0.178184	0.125995		secretion	1.431338	0.490043	0.346513		expression	0.928492	0.336764	0.238128		expression	2.960848	1.809609809	1.279728788		secretion
	exo	0.223674	0.153525	0.108559		secretion	1.019962	0.692336	0.489555		secretion	0.649679	0.058784	0.041566		secretion	0.1936	0.195513194	0.138248706		secretion
THNSL2	cell	2.468895	1.106281	0.638712		secretion	2.566858	2.806129	1.620119		expression	5.316501	0.058784	0.238128		expression	0.494065	7.41316E-06	4.27999E-06		expression
	exo	0.152066	0.059821	0.034538		secretion	1.747854	1.879861	1.085338		secretion	1.588421	1.790554	1.033777		secretion	0.739887	0.083635653	0.048287067		secretion

Supplementary Table 4. The PK
(pharmacokinetics/pharmacodynamics) parameters of ATB1094

ATB1094	IV	PO	SC	IP
Dose (mpk)	1	5	10	10
T _{max} (h)	0.3	0.3	0.3	0.3
T _{1/2} (h)	0.4	0.4	1.1	2.5
C _{max} (ng/ml)	154	504.2	884.2	3722.8
AUC _{last} (h*ng/ml)	124	296.3	1685.2	2533
F (%)		47.8	1.35	2.04