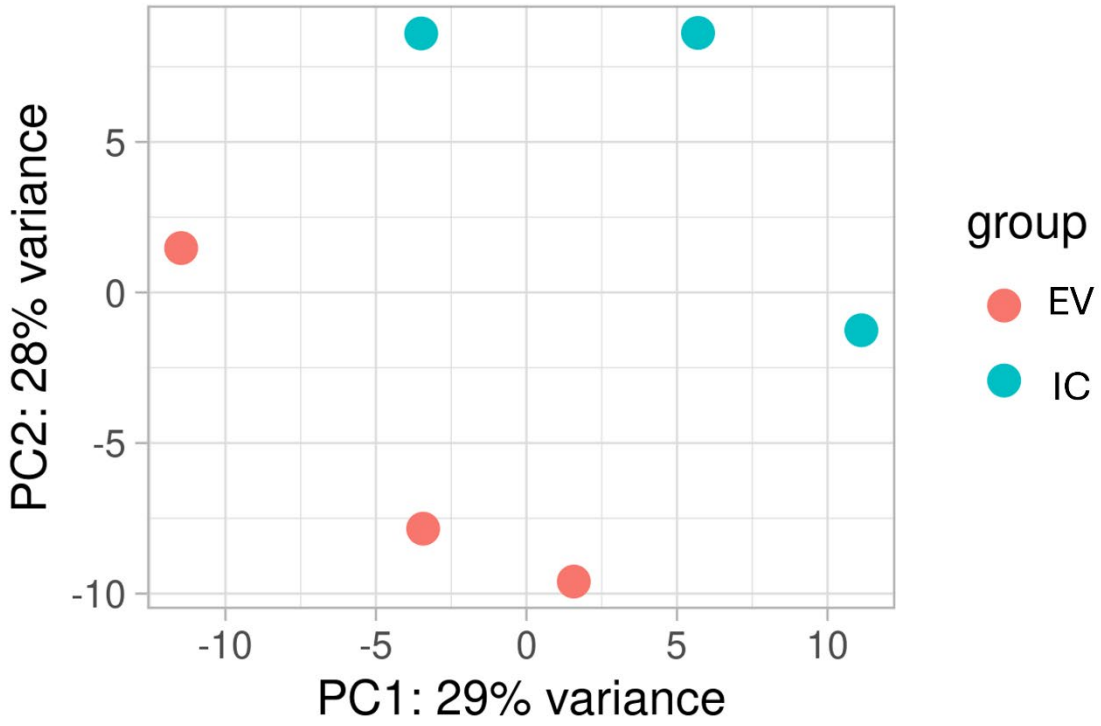


Figure S1. Results of clustering using principal component analysis of DeSeq number of genes from IC (n=3) and EV (n=3). The numbers on the axes represent the percentage of total variance explained by the first and second PC. Principal Component Analysis (PCA) was performed on the variance-stabilised and batch-corrected counts using the DESeq2 package. The removeBatchEffect limma function was applied to remove variation attributable to the 'day' covariate. The resulting data was projected onto its first two principal components using the top 200 most variable genes, and visualised while annotating for 'condition'.

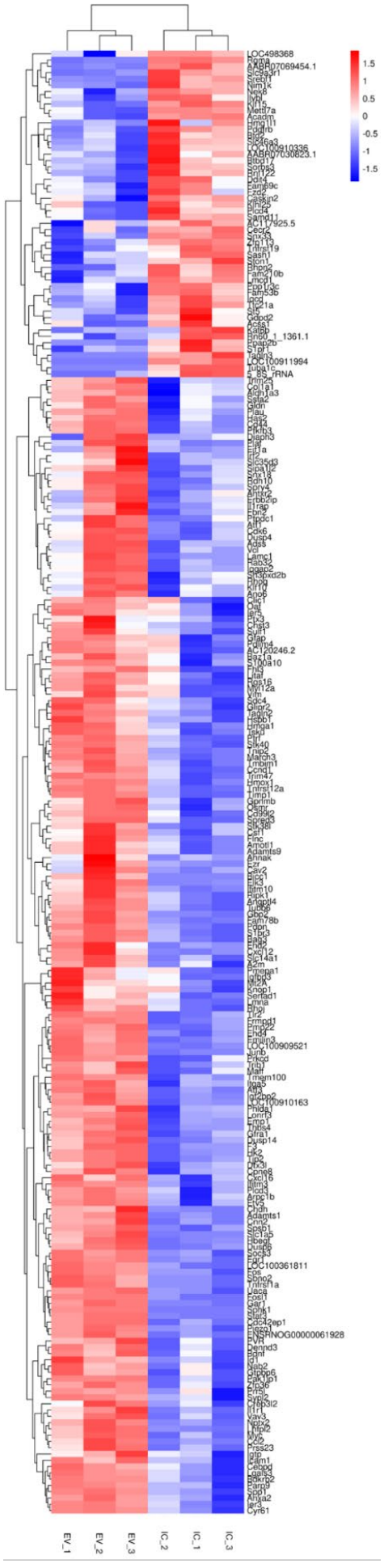

1.5
1
0.5
0
-0.5
-1
-1.5
EV_1
EV_2
EV_3
IC_2
IC_1
IC_3

Figure S2. Transcriptomic profiling of IC_vs_EV comparison group. Heatmaps of differentially expressed genes (DEGs) were obtained using pheatmap R package. Each row represents a gene and each column corresponds to an individual sample, sample groups indicated by column annotations. Gene expression values were row-scaled, hierarchical clustering was performed for both rows (genes) and columns (samples) using Euclidean distance and the complete clustering method. The color scale represents scaled expression values and ranges from blue (down-regulated) to red (up-regulated).

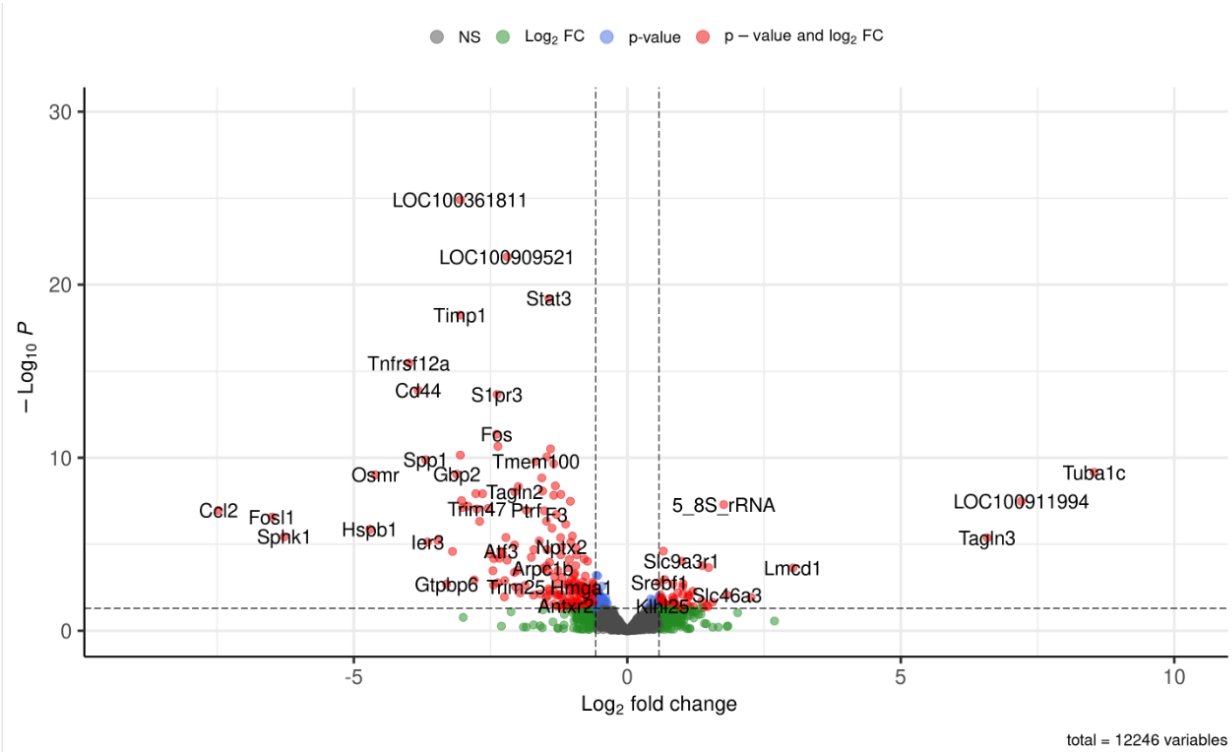


Figure S3. Volcano plot showing the level of gene expression depending on the fold change and p-value (p<0.05 and |FC|<1.5), the expression of genes in the control group is shown relative to the ex-perimental group, FC<1.5 – down-regulated genes, FC>1.5 – up-regulated genes in the comparison group IC_vs_EV.

Pathway	Gene ranks	NES	pval	padj
Focal adhesion		-1.96	$3.4 \cdot 10^{-5}$	$2.3 \cdot 10^{-3}$
Integrin mediated cell adhesion		-1.90	$1.9 \cdot 10^{-4}$	$3.3 \cdot 10^{-3}$
Interactions between CFTR and other ion channels		1.34	$2.4 \cdot 10^{-4}$	$3.4 \cdot 10^{-3}$
TNF alpha NF kB signaling pathway		-1.76	$4.0 \cdot 10^{-4}$	$5.0 \cdot 10^{-3}$
MAPK signaling pathway		-1.64	$7.9 \cdot 10^{-4}$	$7.0 \cdot 10^{-3}$
Estrogen signaling		-1.85	$1.5 \cdot 10^{-3}$	$1.1 \cdot 10^{-2}$
Apoptosis modulation by HSP70		-1.74	$6.2 \cdot 10^{-3}$	$3.2 \cdot 10^{-2}$
Brain derived neurotrophic factor		-1.67	$9.1 \cdot 10^{-3}$	$4.1 \cdot 10^{-2}$
mRNA processing		-1.54	$1.1 \cdot 10^{-2}$	$4.6 \cdot 10^{-2}$
Nucleotide metabolism		-1.67	$1.2 \cdot 10^{-2}$	$4.8 \cdot 10^{-2}$
Oxidative stress response		-1.64	$1.9 \cdot 10^{-2}$	$6.5 \cdot 10^{-2}$
Wnt signaling pathway and pluripotency		-1.48	$4.1 \cdot 10^{-2}$	$1.1 \cdot 10^{-1}$

0 2500 5000 7500 10000

Figure S4. Gene set enrichment analysis (GO-base) in the comparison group IC_vs_EV.

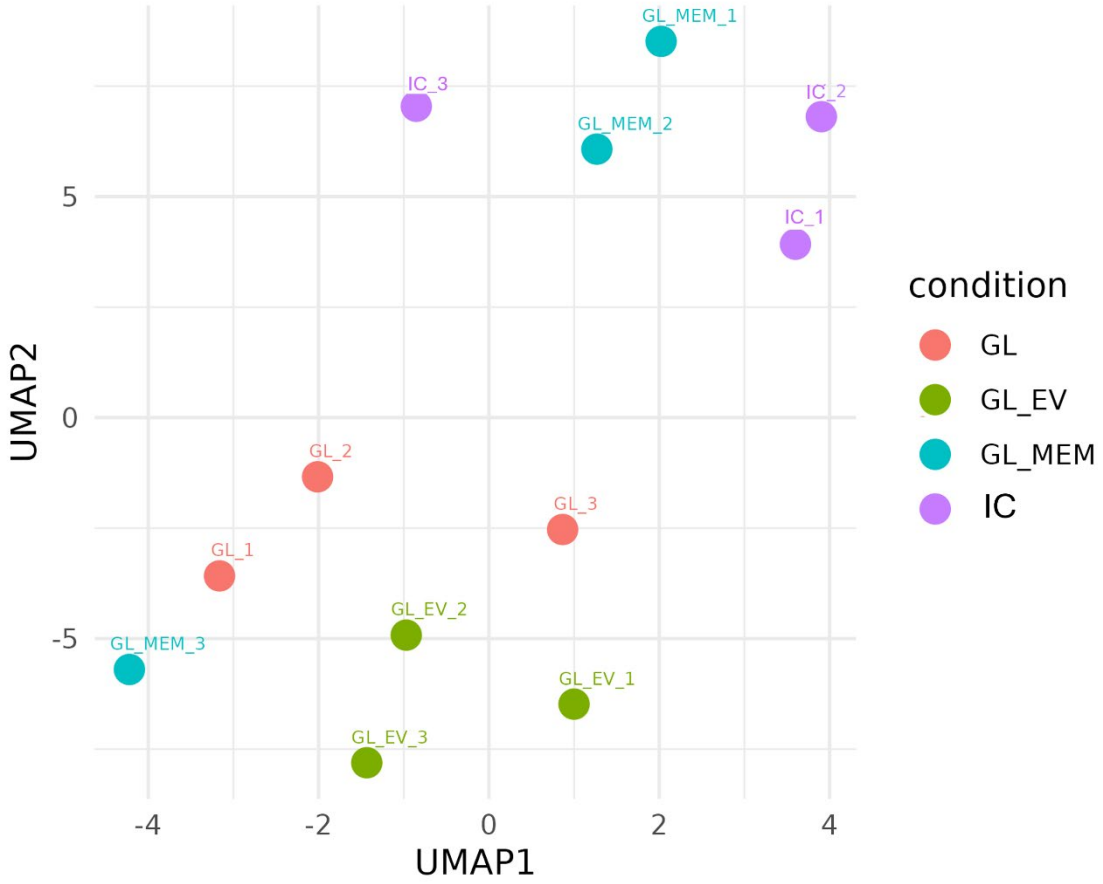


Figure S5. Results of clustering of DeSeq number of genes from IC (n=3), GL, GL_Mem (n=3) and GL_EV (n=3). Two-dimensional UMAP was obtained with umap R package using the top 200 most variable genes identified from the variance-stabilized and batch-corrected counts, with UMAP parameters specifically configured to a neighborhood size of 6, a minimum distance of 1, a spread of 3, and a cosine distance metric.

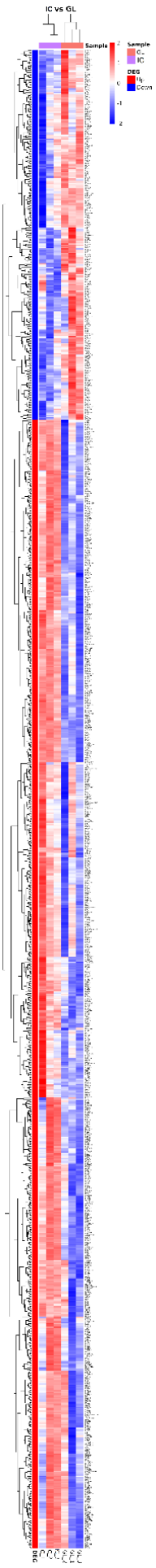

IC vs GL
Sample
Sample
GL
IC
DEG
Up
Down
2
0
-1
-2

Figure S6. Transcriptomic profiling of IC_vs_GL comparison group. Heatmaps of differentially expressed genes (DEGs) were obtained using pheatmap R package. Each row represents a gene and each column corresponds to an individual sample, sample groups indicated by column annotations. Gene expression values were row-scaled, hierarchical clustering was performed for both rows (genes) and columns (samples) using Euclidean distance and the complete clustering method. The color scale represents scaled expression values and ranges from blue (down-regulated) to red (up-regulated).

GL_MEM vs GL
Sample
Sample
GL
GL_MEM
DEG
Up
Down
1
0
-1

Figure S7. Transcriptomic profiling of GL_Mem_vs_GL comparison group. Heatmaps of differentially expressed genes (DEGs) were obtained using pheatmap R package. Each row represents a gene and each column corresponds to an individual sample, sample groups indicated by column annotations. Gene expression values were row-scaled, hierarchical clustering was performed for both rows (genes) and columns (samples) using Euclidean distance and the complete clustering method. The color scale represents scaled expression values and ranges from blue (down-regulated) to red (up-regulated).

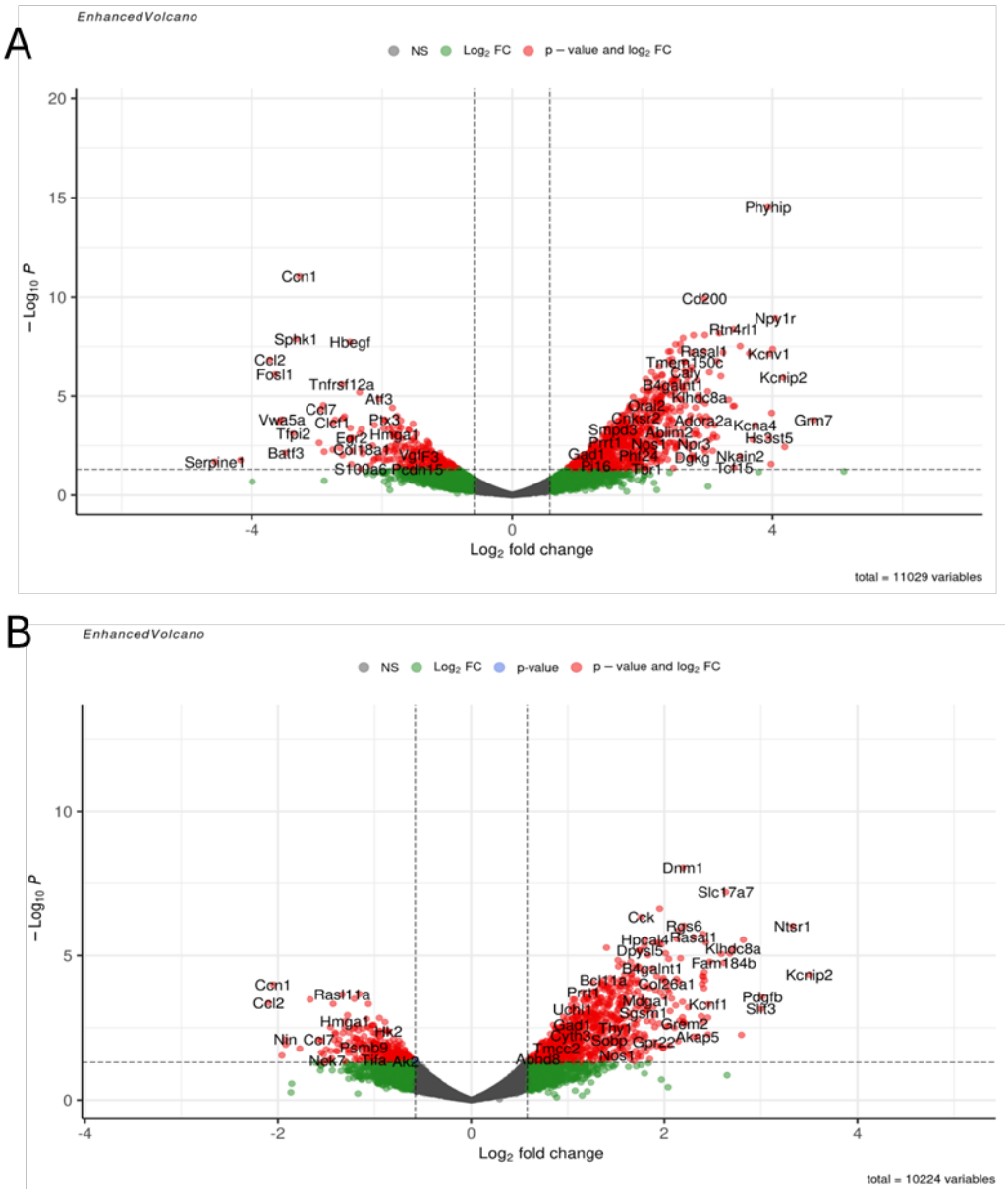


Figure S8. Volcano plot showing the level of gene expression depending on the fold change and p-value (p<0.05 and |FC|<1.5), A, B – Volcano plots showing the gene expression level depending on the fold change and p-value (p-value <0.05 and |FC|<1.5) in the comparison groups IC_vs_GL (A), GL_Mem_vs_GL (B).

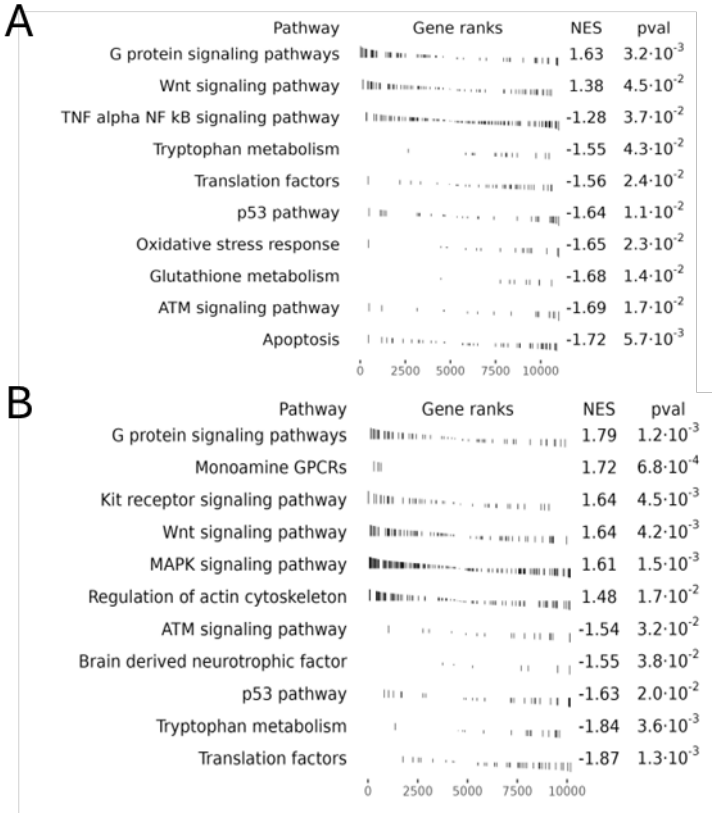


Figure S9. Gene set enrichment analysis (GO-base) in the comparison group IC_vs_GL (A) and GL_Mem_vs_GL (B).

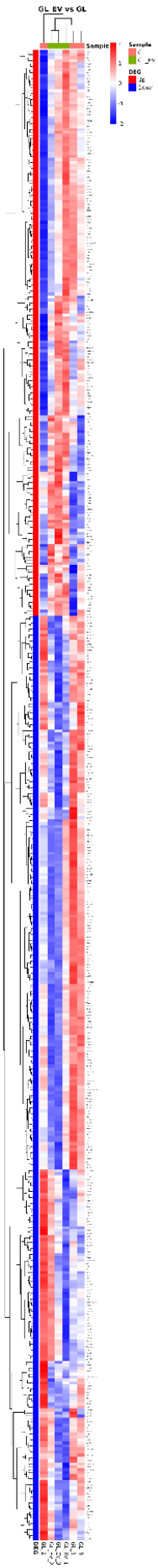

GL_EV vs GL
Sample
Sample
DEG

Figure S10. Transcriptomic profiling of GL_EV_vs_GL comparison group. Heatmaps of differentially expressed genes (DEGs) were obtained using pheatmap R package. Each row represents a gene and each column corresponds to an individual sample, sample groups indicated by column annotations. Gene expression values were row-scaled, hierarchical clustering was performed for both rows (genes) and columns (samples) using Euclidean distance and the complete clustering method. The color scale represents scaled expression values and ranges from blue (down-regulated) to red (up-regulated).

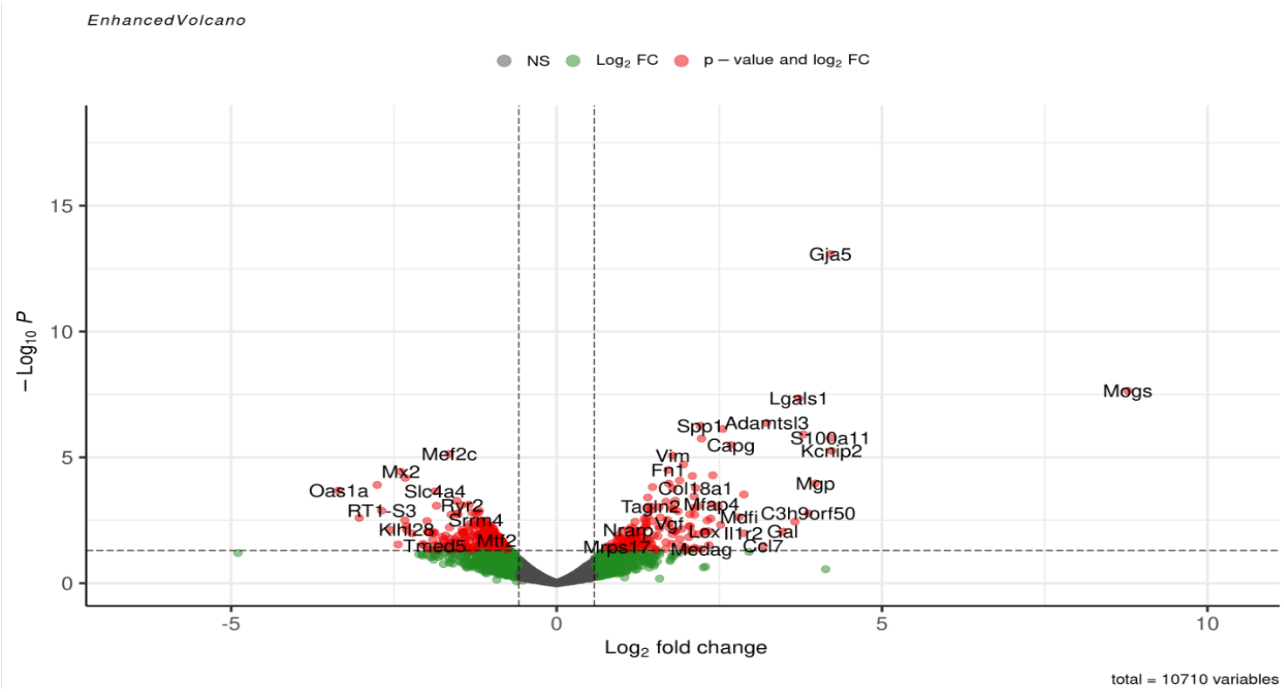


Figure S11. Volcano plot showing the level of gene expression depending on the fold change and p-value ($p<0.05$ and $|FC|<1.5$), the expression of genes in the control group is shown relative to the ex-perimental group, $FC<1.5$ – down-regulated genes, $FC>1.5$ – up-regulated genes in the comparison group GL_EV_vs_GL.

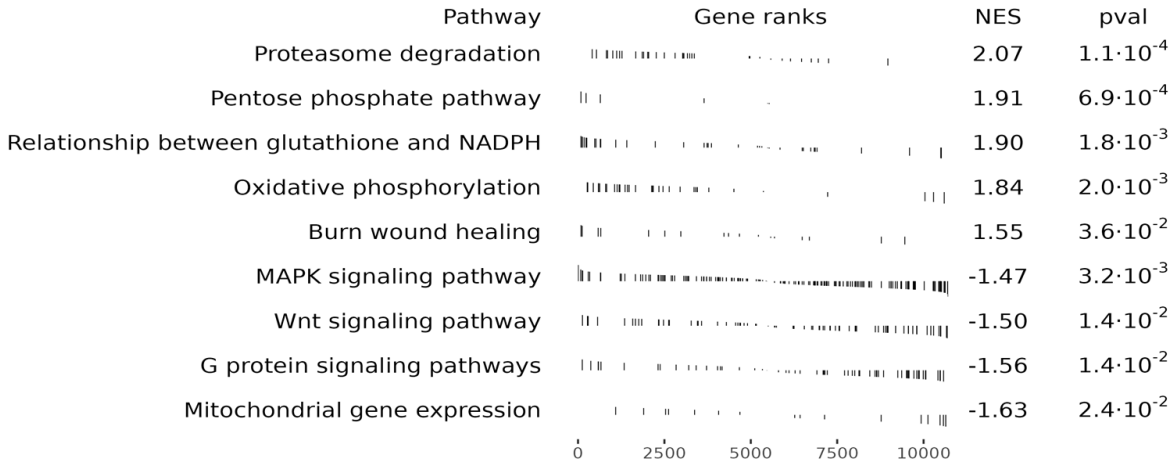


Figure S12. Gene set enrichment analysis (GO-base) in the comparison group GL_EV_vs_GL.

Up/Down-regulated	**Name of the gene**	**Description**	**GO_Biological processes**

Up-regulated	*Elk3*	transcription factor of cell cycle, cell growth and neural tissue development [1]	wound healing
	Tnfrsf12a	receptor that activates various pathways in neurons[2]	
	Timp1	inhibitor of metalloproteinases responsible for the survival and neuroprotection of neurons [3]	
	Anxa2	gene is critical for axonal growth and cytoskeletal stabilization in neurites [4]	
	Vcl	gene controls axon growth through interaction with the extracellular matrix [5]	
	F3	gene controls axon growth through interaction with the extracellular matrix [6]	
	Tsku	gene interacts with molecules involved in Wnt signaling and TGF-beta signaling [7]	
	Hk2	gene controls glucose metabolism and energy production [8]	response to hypoxia
	Hmox1	gene that controls redox balance and is involved in various cellular processes, including antioxidant defense and antiapoptosis [9]	
	Stat3	gene stimulates the synthesis of genes responsible for reducing ROS [10]	
	Il1rap	interleukin-1 receptor, which in neurons is involved in the development and maintenance of synapses [11]	cytokine-mediated signaling pathway
	Cd44	receptor that binds to hyaluronic acid and is responsible for axonal growth [12]	
	Ccl2	gene is necessary for synapse function and is also involved in neuropeptide transduction [13]	
	Cxcl12	chemokine that controls migration processes, the direction of axon growth, and interactions with other cells [14]	
	Tnfrsf1a	TNF receptor, the activation of which leads to the induction of many processes associated with inflammation, neuroprotection and cell homeostasis [15]	
	Egr1	gene responsible for signals in the synaptic cleft and synaptic plasticity [16]	
	Antxr2	gene remodels extracellular matrix [17]	extracellular matrix organization
	Adamts1	gene remodels extracellular matrix [18]	
	Pmp22	gene helps maintain the myelin sheath around the processes [19]	
	Has2	hyaluronic acid synthetase [20]	
	Sulf1	gene modifies heparan sulfate, thereby being able to modify various signaling pathways [21]	
	Sh3pxd2b	gene controls the actin cytoskeleton and cell adhesion [22]	cell-substrate adhesion

	Arpc1b	gene that controls actin polymerization and cell migration [23]	actin filament organization
	Tagln2	control the growth of dendritic spines and the elongation of axons [24]	
	Spred3	Ras/MAPK cascade inhibitors [25]	ERK1 and ERK2 cascade
	Dusp6	Ras/MAPK cascade inhibitors [26]	
	Glipr2	activators of the pathway that stimulates the development and survival of neurons [27]	
	Gpnmb	activators of the pathway that stimulates the development and survival of neurons [28]	
	Atf3	gene activated by the ERK1 and ERK2 cascade and stimulating cell proliferation [29]	
	Trim25	activator of NF-kappa B signaling pathway [30]	canonical NF-kappaB signal transduction
	Ier3	activator of NF-kappa B signaling pathway [31]	
	Hspb1	gene protectes against reactive oxygen species and the elimination of proteins damaged by it [32]	response to reactive oxygen species
	Prkcd	kinase that controls the balance between cell death and survival [33]	
	Stk38l	gene controles microtubule reorganization and neurite growth [34]	regulation of cellular catabolic process
	Snx18	gene regulates the development of the axonal cone [35]	regulation of neurogenesis
	Nab2	gene controls axon growth and dendrite branching [36]	
	Gfap	gene controles maintaining the structure and function of astrocytes [37]	gliogenesis
	Tmbim1	transmembrane subunit of the BAX inhibitor - regulates the level of intracellular calcium, and also blocks the action of the proapoptotic protein Bax [38]	
	Bag3	gene controls the formation of autophagosomes and stabilizes the functioning of mitochondria [39]	negative regulation of apoptotic signaling pathway
	Bdnf	gene plays a vital role in supporting the growth and survival of neurons in the brain	regulation of autophagy
	Mycn	gene acts as a transcription factor, influencing gene expression related to cell growth, proliferation, and differentiation [40]	regeneration

	Chst3	the chondroitin 6-O-sulfotransferase 1 gene, which is responsible for modifications of chondroitin sulfate proteoglycans needed for the regeneration of neuronal processes [41]	
	Creb3l2	transcription factor involved in neuroregeneration, particularly by promoting neurite outgrowth and neuronal differentiation [42]	

Table S1. Lists of the most significant down-regulated differentially expressed genes (DEGs) associated with enriched biological pathways in the IC_vs_EV comparison group.

Up/Down-regulated	Name of the gene	Description	GO_Biological processes
Up-regulated	*Trpv2, Nell2, Thy1, Kiaa0319*	gene's proteins are found in the axonal cone and provide guidance for axon growth [43–46]	axonogenesis
	Rtn4rl1	gene is an active participant in axon regeneration [47]	
	Slit2	gene is responsible for axon navigation, inhibiting its growth in the wrong direction [48]	
	Ptpro	gene controls axon elongation and branching in response to BDNF [49]	
	Robo2	Robo-signaling protein responsible for axon elongation [50]	
	Epb41l3, Epha4, Ephb6, Ephx4	the ephrin family genes are responsible for axon elongation [51]	
	Snap25	synaptovesicle protein [52]	regulation of synapse structure or activity
	Shank2, Shank1	synaptic scaffold proteins, to control receptor positioning [53]	
	Lrfn1, Dlg4, Arhgap33	genes control synaptic plasticity and structure control [54–56]	
	Kidins220, Celsr2, Bcl11a	dendrite formation genes [57–59]	dendrite development
	Nos1	nitric oxide (NO) synthetase, which acts as a signaling messenger in various neural processes [60]	neurotransmitter transport
	Adora2a	receptor that influence the release of various neurotransmitters, including glutamate, dopamine and GABA [61]	
	Slc16a2	thyroid hormone transporter [62]	
	Slc17a6 , Slc17a7	glutamate transporters [63]	

	Slc2a3, Slc2a6	glucose transporters [64]	
	Stxbp5	neurotransmitter exocytosis regulator [65]	
	Iqsec3	gene participates in the regulation of the postsynaptic membrane in GABAergic synapses [66]	postsynapse organization
	Itpka	one of the subunits of postsynaptic kinases that respond to activation of receptors on the postsynaptic membrane [67]	
	Grip2	the major protein of scaffolds on the postsynaptic membrane that controls the location of AMPA-kainate receptors [68]	
	Ppfia2, Ppfia3, Ppfia4, Rims1, Unc13a	proteins form presynaptic terminals by regulating the fusion of synaptic vesicles with the membrane [69]	positive regulation of synaptic transmission
	LRRTM1, Cnksr2, Dact1	genes responsible for synapse structuring and formation [70,71]	
	Syp	gene modulates the function of the synapse, which controls vesicle fusion and neurotransmitter exocytosis [72]	
	Rasgrf1	a protein in the Ras signaling pathway that is responsible for the response to calcium influx at the postsynaptic membrane [73]	
	Gria4, Gria1	glutamate receptor subunits [74]	glutamate receptor signaling pathway
	Grin1, Grin2d	NMDA receptor subunit genes that respond to glutamate [75]	
	Camk1g, Camk2a, Camk2b, Camk2d, Camkk1	Ca2+/calmodulin-dependent protein kinase genes, which are responsible for the membrane depolarization response [76]	regulation of membrane depolarization
	Tspoap1	gene influences the localization of voltage-gated channels [77]	regulation of metal ion transport
	Kcnip1 , Kcnip2, Kcnip4	Potassium ion voltage-gated channel proteins [78]	
	Fxyd6, Fxyd7	proteins that control the work of Na+/K+-ATPase [79]	
	Atp1a3, Atp1b1	Na+/K+-ATPase subunit proteins [80]	
	Atp2b2, Atp2b3, Atp2b4	Plasma membrane Ca2+ transporting ATPase (PMCA2) plays a critical role in neurons by regulating calcium ion concentrations [81]	calcium ion transport

	Rell2	gene for a transmembrane protein that activates Rell signaling [82]	positive regulation of cell-substrate adhesion
	Thy1	CD90 protein is a membrane protein that controls axonal growth by anchoring it to the extracellular matrix [83]	
	Foxg1, Rnf112, Parp6	genes involved in neuronal development [84–86]	positive regulation of nervous system development
	Pdgfb	astrocyte proliferation stimulating protein [87]	gliogenesis
	Bmerb1, Carmil2, Carmil3	proteins that regulate actin polymerization and signaling pathways in neurons [88,89]	actin filament organization
	mTOR	autophagy regulating protein [90]	negative regulation of neuron apoptotic process
	Agap2	gene stimulates neuronal survival processes by activating the PI3K/Akt pathway [91]	
Down-regulated	*Hmox1, Serpine1*	hypoxia response protein [92]	response to hypoxia
	Pmaip1	proapoptotic protein, inhibitory anti-apoptotic protein Mlc-1 [93]	
	Limd1	Hif-1alpha inhibitory gene [94]	
	Lif, Vrk2, Sphk1, Klf6	activators of cell survival pathways [95–98]	cellular response to chemical stress
	Fos, Sesn2, Gdf15	a marker of cellular response to stress [99–101]	
	Hsp90b1	heat shock protein that responds to the accumulation of misfolded proteins [102]	
	Rest, Bmp4	protein activated by oxidative stress [103,104]	
	Bdkrb2	bradykinin receptor that triggers neuroinflammation processes [105]	
	Trib1, Fosl1	genes that are activated by different types of stress, such as DNA damage from reactive oxygen species [106,107]	cellular response to oxidative stress
	Nfe2l2, Prdx1, Pex2	genes for proteins that neutralizes reactive oxygen species, thereby protecting cells [108–110]	
	Dnajc3, Pdia4	genes are activated by ER stress [111,112]	response to endoplasmic reticulum stress
	Anxa1, Hells	their expression is increased during apoptosis [113,114]	regulation of apoptotic signaling pathway
	Ier3, Fas, Tnfrsf12a	genes that are activated by any type of stress, stimulating apoptosis [115,116]	

	Tpt1	a gene that controls both cell survival and cell death pathways [117]	
	Lgals3	galectin-3 protein, which is activated by glutamate excitotoxicity and triggers autophagy and apoptosis processes [118]	
	Spry2	gene reacts to a decrease in oxygen by activating cell death processes [119]	
	Klf4	a gene for a protein that enhances the response to oxidative stress, thereby stimulating apoptosis [120]	
	Cdkn1a, Csrp1	a gene that is activated in response to cell damage and stimulates its repair [121,122]	wound healing
	Nrg1	gene actively participates in the development of neurons and in the restoration of synapse function [123]	
	Tfpi2, Rhoc	genes activated by axonal injury [124,125]	
	Fgf2	cell division stimulating growth factor [126]	
	Egr2, Etv5, Nin, Sox10, Sox8	proteins that control neurite elongation [127–130]	regulation of neurogenesis
	Nkx2-2, Notch1	proteins stimulate regeneration [131,132]	
	Sdc4, Cxcl12	genes responsible for intercellular adhesion and migration [133,134]	regulation of cell-cell adhesion
	Has2	gene controls synthesis of hyaluronic threads [20]	extracellular structure organization
	Piezo1	mechanotransduction gene activated by neuronal adhesion [135]	
	Gadd45b, Gadd45g, Gadd45a	genes for subunits of phosphatase that inhibits the MAPK kinase cascade [136]	negative regulation of phosphorylation
	Ppp1r15a	a gene that is activated in response to various types of cellular stress, including oxidative stress [137]	
	Cdkn2c, Cdkn2b	inhibitors of CDK4 and CDK6, thereby inhibiting the cell cycle [138]	

Table S2. Lists of the most significant differentially expressed genes (DEGs) associated with enriched biological pathways in the IC_vs_GL and GL_Mem_vs_GL comparison groups.

Up/Down-regulated	Name of the gene	Description	GO_Biological processes
Up-regulated	*Elk3, Timp1, Anxa2*	genes stimulate wound healing by enhancing proliferation, elongating processes and inhibiting apoptosis [139–141]	wound healing
	Fgr	tyrosine kinase that activates NF-κB and ERK1/2 pathways [142]	phosphatidylinositol 3-kinase/protein kinase B signal transduction
	Txn1	thioredoxin, which acts as an antioxidant, thereby protecting against oxidative stress [143]	
	Axl	Gas6 receptor, activation of which also promotes survival [144]	
	Metrn	gene responsible for the elongation of axons [145]	regulation of axonogenesis
	Crabp2	gene participates in axon regeneration [146]	regulation of axonogenesis
	Fbln2	a gene encoding an extracellular matrix protein that is involved in the outgrowth of the dendritic tree [147]	cell-substrate adhesion
	Lgals1	galectin, which is actively expressed in neurons and is responsible for the interaction between cells of the nervous tissue [148]	cell-substrate adhesion extracellular matrix organisation
	S100a10	it is involved in the regulation of serotonin receptor traffic, glutamatergic transmission and calcium signaling in neurons [149]	
	Fn1	fibronectin, a key component of the brain's extracellular matrix	
	Adamts7	a metalloproteinase that can degrade components of the extracellular matrix [150]	extracellular matrix organisation actin filament organisation
	Vwa1	gene is actively expressed at the ends of neurites and interacts with the extracellular matrix [151]	
	Arpc1b	a protein responsible for the branching of the actin cytoskeleton and thus for the branching of neurites [152]	
	Tpm2	gene controls the formation of axons and dendrites, the elongation of nerve cell processes [153]	actin filament organisation gliogenesis
	Tspo	gene responsible for astrocyte proliferation [154]	
	Olig1	gene activates oligodendrocytes and stimulates the protection of neuronal processes [155]	gliogenesis response to reactive oxygen species
	Nptxr	pentraxin, which controls synapse formation and the flow of ions into neurons [156]	
	Pex5	gene involved in the formation of peroxisomes [157]	response to reactive oxygen species cellular response to oxidative stress
	G6pd	gene involved in cellular respiration and synthesis	
	Coa8	electron transport chain gene cytochrome c oxidase-binding [158]	

	Lcn2	gene participates in the control of neuronal responses to external stimuli [159]	cellular response to oxidative stress reactive oxygen species metabolic process
	Spp1	gene is associated with cell survival and axon reorganization upon injury[144]	response to axon injury
	Tesc	gene controls the entry of metal ions into neurons, especially calcium ions, by binding to it [160,161]	regulation of metal ion transport
	Hspa2	heat shock protein gene, which is involved in ion transport by binding to the CatSper ion channel [161]	regulation of metal ion transport peptide hormone secretion
	Kcnip2	Potassium ion voltage-gated channel [78]	
	Best1	calcium-activated anion channel, meaning it allows chloride ions to pass through cell membranes in response to changes in intracellular calcium levels [162]	
	Fxyd5	gene regulates the work of Na+/K+-ATPase [163]	
	Rbp4	gene participates in the transport of retinoic acid [164]	
	Npy	a neuropeptide essential for the survival of neurons [165]	peptide hormone secretion
	Scn1b	voltage-gated sodium channel beta-1 subunit (VGSC) [166]	regulation of membrane depolarisation
	Auts2, Tnr, Septin7	genes regulate of axon and neurite growth [167–169]	axonogenesis
Down-regulated	*Ttc3 , Vangl2 , Nfib*	genes inhibit the emergence of neurites and the elongation of axons [170–172]	axonogenesis regulation of cellular response to stress
	Kif5c , Kif5b, Mapt	genes responsible for transport in axons and dendrites [173,174]	
	Tmem33	an ER stress-induced molecule that modulates the unfolded protein response signaling cascade leading to apoptosis [175]	
	Pum2	gene responsible for axon regeneration in response to stress [176]	regulation of cellular response to stress dendrite development
	Hgf	gene stimulates neuronal survival in response to injury [177]	
	Nfe2l1	gene activated by ER stress [178]	
	Nek1	gene plays a key role in the response to DNA damage [179]	
	Foxo1	one of the key genes in the response to oxidative stress [180]	
	Ino80	gene responsible for the repair of double-strand DNA breaks [181]	
	USP13	gene plays a role in various cellular processes in neurons, including regulation of protein degradation and axonal degeneration [182]	

	Mef2c	a gene encoding a protein that regulates the formation of dendritic spines, which stimulates the elimination of spines during excitotoxicity [183]	
	Pak3	gene participates in the formation of dendritic spines [184]	dendrite development
	Ppp1r9a	gene responsible for the creation of protein scaffolds in the synapse [185]	regulation of synapse organization
	Tnik , Zfp804a , Tanc2	genes responsible for regulating the structure and function of synapses [186–188]	regulation of synapse organization
	Ntrk2 , Ephb1 , Sema5a , Cxcl12	genes are necessary for the correct direction of axon growth [189–191]	axon guidance
	Mycbp2 [192]	gene is involved in axon degradation	axon guidance
	Atp2b4, Atp2b1, Atp1a2, Ryr2, Camk4	genes of ion transporters that control the transport of calcium ions into the cytoplasm of neurons	regulation of calcium ion transport
	Baz1a , Kdm5a , Smarca2	genes that control DNA remodeling [193–195]	negative regulation of gene expression, epigenetic
	Limch1, Pde4d	gene play a role in regulating cell motility [196,197]	actin-mediated cell contraction
	Cacna1c, Cacna1d, Cacna2d1	subunits of voltage-dependent calcium channel [198]	calcium ion transmembrane transport via high voltage-gated calcium channel
	Kif3a, Map1a	genes of motor proteins responsible for cargo transport from axons and dendrites [199,200]	axo-dendritic protein transport

Table S3. Lists of the most significant differentially expressed genes (DEGs) associated with enriched biological pathways in the GL_EV_vs_GL comparison group.

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