Supplementary Information S2 | **Role of GRPs in development, tissue and organ homeostasis**

Knockout Site	Mutant Mouse Model*	KO	Key Phenotypes	Refs.
Whole body	*Grp78*$^{-/-}$	-/-	Embryonic lethality at E3.5 Proliferation↓, apoptosis↑	1
	Grp78$^{+/-}$	+/-	Viable, normal phenotype, Ig production normal GRP94↑, PDI↑ Suppress HFD-induced acute pancreatitis	1 2
	Grp78$^{+/-}$ (C57BL/6)	+/-	HFD-induced obesity and insulin resistance↓, UPR (adipose)↑ Suppress experimentally induced arthritis T cell proliferation↓, suppress cytotoxic T cell phenotype	3 4 5
	BiP (ΔKDEL)-HA (knockin)	-/-	Pulmonary surfactant biosynthesis↓, neonatal respiratory failure	6
	Grp94$^{-/-}$ (exon 1 disruption)	-/-	Embryonic lethality at E7-10.5 Blocks cardiomyocyte differentiation IGF-1↓, integrin↓, GRP78↑, CNX↑, CRT↑, XBP-1s↓	7
	Grp94$^{-/-}$ (exon 3 disruption)	-/-	Embryonic lethality at E.7 Blocks mesoderm induction, IGF-II production↓	8
	ORP150$^{+/-}$	+/-	Survival to kainate↓	9
Inducible knockout, adult bone marrow and other organs	*Grp78*$^{f/f}$; *Mx1-Cre*	-/-	Hematopoietic stem cells↓, lymphoid progenitors↓, viability↓ Cytokine and chemokine secretion↑↓ UPR↑, apoptosis↑ in bone marrow	10
	Grp94$^{f/f}$; *Mx1-Cre*	-/-	Loss of HSC niche attachment, HSC↑ Alters myeloid and lymphoid differentiation, viability↓ Surface integrin α-4↓, Ms4a3↓, Cx32↓, PIP3↑, pAKT↑ in HSCs	11 12
	Hsp90b1$^{f/f}$; *Rosa26*$^{ERT-Cre}$	-/-	Hematochezia, small intestinal defect Diarrhea, weight loss, postnatal death (D12-14)	13
B cells	*Hsp90b1*$^{f/f}$; *CD19-Cre*	-/-	Toll-like receptor response↓ Normal B cell function	14

Macrophage	*Hsp90b1*$^{f/-}$; *Lys-Cre*	-/-	Toll-like receptor response↓ Endotoxin shock↓, acute infection↑	15
Adipose	*Grp78*$^{f/f}$; *aP2-Cre*	-/-	Lipoatrophy, insulin sensitivity↑ ER expansion viability↓	16
Muscle	*Grp94*$^{f/f}$; *MCK-Cre*	-/-	IGF↓, muscle and body growth↓	17
Liver	*Grp78*$^{f/f}$; *Alb-Cre*	-/-	Fatty liver, moderate liver injury Exacerbates acute and chronic liver disease	18 19
	Grp94$^{f/f}$; *Alb-Cre*	-/-	Minor liver injury, disrupts cell adhesion protein organization Liver progenitor cell proliferation↑	20
Oocyte	*Hsp90b1*$^{f/f}$; *Zona pellucida 3-Cre*	-/-	Fails to reach 2 cell stage Abnormal mitotic spindle	21
Prostate epithelium	*Grp78*$^{f/f}$; *Probasin Cre*	-/-	Normal	22
Intestinal epithelium	*Grp78*$^{f/f}$; *Ah1-Cre*	-/-	ER stress↑, loss of intestinal epithelial stemness Rapid repopulation by GRP78 positive, unrecombined cells	23
	Hsp90b1$^{f/f}$; *Villin-Cre*	-/-	Wnt signaling↓, gut proliferation defect↓, postnatal death	13
Purkinje cells	*Grp78*$^{f/-}$; *pc-Cre*	-/-	GRP94↑, PDI↑, CHOP↑, GADD34↑, peIF2α↓ ER dilution, cytosolic ubiquitination↓, cerebellar atrophy, growth retardation	24
	Grp94$^{f/-}$; *pc-Cre*	-/-	Normal	24
Endothelial cells	*Grp78*$^{f/+}$; *Tie2-Cre*	+/-	Normal organ microvessel density Tumor angiogenesis↓, melanoma metastatic growth↓	25
Whole body (over-expression)	*ORP150-Tg*		Vacuolar degeneration in the mouse myocardium Abetalipoproteinemia	26 27
Neuronal (over-expression)	*ORP150-Tg*		Glutamate toxicity↓, survival↑	9
	ORP150-Tg		Purkinje cell↑, cerebellar function↓	28

**Hsp90b1* is also known as *Grp94*.

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