

## Supplementary Material

**Table S1.** Summary of the main metabolic pathways regulating HSC functions.

Pathway	Young or steady-state HSCs	Stress or aged HSCs	Key regulators/mechanisms	Citations
Glycolysis	Supports quiescence and limits mitochondrial dependence	Stress increases glycolytic demand. Aging reduces metabolic flexibility	HIF-1 $\alpha$ , MEIS1, PDK, PFKFB3	[1,2]
Oxidative phosphorylation	Restrained but still required for HSC maintenance	Increased or dysregulated with aging; causes mitochondrial stress and altered resilience	Mitochondrial ATP, SDHAF1, SIRT7/UPRmt	[3–5]
Fatty acid oxidation/lipid metabolism	Supports HSC maintenance, self-renewal, and asymmetric division	Altered lipid handling may affect mitochondrial fitness and stress adaptation	PML-PPAR $\delta$ , CPT1, CD36	[6–8]
BCAA/amino acid metabolism	Helps maintain amino acid balance and HSC fitness	Dysregulated amino acid availability or catabolism may impair replication-dependent HSC function	BCAA catabolism	[9]
Pentose phosphate pathway/NADPH balance	Supports redox balance and cell growth	Important during oxidative or regenerative stress.	G6PD, NADPH	[5,10,11]
NAD <sup>+</sup> metabolism	Supports mitochondrial function, DNA repair, and stress resistance	NAD <sup>+</sup> decline or CD38-driven NAD <sup>+</sup> consumption contributes to aged HSC dysfunction	NAD <sup>+</sup> , CD38, SIRT proteins, PARPs	[12,13]
Autophagy/mitophagy	Maintains quiescence and metabolic quality control by clearing mitochondria	Declines or becomes insufficient with aging, allowing mitochondrial/metabolic stress to accumulate	ATG pathways, mitochondrial clearance, SIRT3	[14–16]
Lysosomal function/CMA	Supports protein quality control and HSC activation capacity	Lysosomal and CMA dysfunction contribute to aged HSC defects	LAMP2A, HSC70, lysosomal activity, CMA activation	[17–19]
Mitochondrial ROS control	Low ROS supports quiescence and long-term HSC potential	Increased ROS promotes DNA damage, differentiation bias, and functional decline	FOXO proteins, SIRT3, mitochondrial homeostasis	[16,20]
IGF1 and niche-derived growth signals	Supports balanced regenerative and mitochondrial responses	Age-associated IGF1 decline in the bone marrow niche contributes to HSC aging	IGF1, niche-derived metabolic support	[21]

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