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# Blood stem cells SEL-ect quiescence

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**Abstract:**

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**Blood stem cells SEL-ect quiescence**

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In this issue of Blood, Liu and colleagues demonstrate that active endoplasmic reticulum associated degradation (ERAD) of misfolded proteins is required to maintain hematopoietic stem cell (HSC) quiescence, and hence proper long-term blood formation [1]. They identify a mechanism by which the Sel1L protein, a key member of the ERAD complex, maintains HSCs in a state of low mTORC1 activity, thereby preventing HSC proliferation. These data implicate that steady-state protein quality control directly contributes to keeping HSCs outside of the cell cycle.

HSCs have immense regenerative potential, as one cell can reconstitute the whole blood system for an entire lifetime. Counterintuitively lifelong blood production can only be achieved if cells divide very infrequently and otherwise reside in a specific state outside of the cell cycle, termed quiescence. Effectively the most quiescent HSCs serve as a reservoir that only contributes to blood production under severe stress. Perturbation of the quiescence to division balance almost inevitably leads to loss of long-term HSC function and is of high clinical relevance in blood disorders ranging from cytopenias to malignancies. Quiescence is an actively maintained state of low metabolism with specific hallmarks shared by all quiescent cells, ranging from bacteria and yeast to mammalian adult tissue stem cells, including HSCs [2]. These hallmarks encompass a preference for glycolytic metabolism, in addition to low levels of transcription, ribosome biogenesis, and protein synthesis. Given HSCs' impressive longevity, it is no surprise that strict quality control mechanisms such as enhanced autophagy and specific DNA damage responses are also essential to maintain optimal genetic integrity and fitness of quiescent HSCs[3].

Once a protein is synthesized, protein folding occurs in the endoplasmic reticulum and is a naturally error-prone process that often results in the generation of misfolded or unfolded proteins. Failure to correctly manage unfolded proteins can culminate in cell death. External stress conditions such as oxidative stress can increase protein misfolding, activating the unfolded protein response (UPR) which relieves endoplasmic reticulum stress via numerous routes, including activation of the Sel1L/Hrd1 ERAD complex, known to target misfolded proteins to proteasomal degradation. Previous work from the Liu group as well as others has demonstrated that an intact UPR pathway is very important to safeguard HSC identity and proper function under stress conditions [4–6].

Here the authors set out to determine whether protein quality control via ERAD needs to remain engaged during quiescence despite the fact that cells have overall low protein synthesis. Their first important finding is that the HSCs that divide the least (as measured by label retaining assays) have lower levels of protein aggregates and higher levels of Sel1L mRNA than HSCs with a higher divisional history. Second, deletion of *Sel1L* via two distinct methods in mice led to a reduction in HSC frequency in the bone marrow and loss of repopulation capacity upon transplantation. *Sel1L* knock-out HSCs displayed an "activated" phenotype, with an increased proportion entering the cell cycle, increased cell size and mTOR activation. The authors then quite elegantly identify Rheb, a regulator of mTOR, as a new protein substrate of the ERAD complex, which fails to be ubiquitinated and degraded by the proteasome in the absence of Sel1L. *Sel1L* deletion thus leads to high levels of mTOR (see figure). Importantly inhibition of mTOR via rapamycin or genetic means rescued HSC numbers and repopulation capacity close to those of wild-type mice.

Altogether this study demonstrate that ERAD-mediated protein quality control mechanisms are essential in HSCs with low protein synthesis to prevent mTOR upregulation and excessive activation. Importantly Liu et al. provide yet another confirmation that the less frequently an HSC divides the more reliant it is on quality control mechanisms, and that these same mechanisms reinforce quiescence. In work published concomitantly to theirs, Xu et al. also found that *Sel1L* deletion leads to loss of repopulating HSC [7]. Focusing on the fact that improper quality control of cell surface proteins may be highly deleterious to HSCs, they identified MPL, the receptor of thrombopoietin, as a target protein of the ERAD complex. *Sel1L* knock-out HSCs accumulated aggregates of misfolded MPL intracellularly, displayed decreased levels of functional MPL on their surface, and could not be retained in their perivascular niche. The mechanistic insights provided by the two groups are highly synergistic as complex interactions with the niche, as well as thrombopoietin itself [8,9], are critical to maintain HSC quiescence. In fact, it is highly likely that ERAD provides folding control for many more molecules that contribute to HSC function. Future studies will thus have to examine what is the physiological range of ERAD activity in the hematopoietic system over a lifetime, especially with aging and following infection or chronic inflammation. Mutations also often change the probability of certain proteins to be misfolded. As such, it wouldn't be surprising if perturbations in proteostatic control pathways contributed to HSC clonal expansions as well as the development and progression of malignancies.

**Figure legend:**
RHEB is normally maintained to low levels in HSCs via Hrd1/Sel1L (ERAD) which targets it for proteasomal degradation, thereby keeping mTORC activation low. When Sel1L is genetically deleted, RHEB is stabilised and mTORC1 activated, leading to HSC loss of quiescence.

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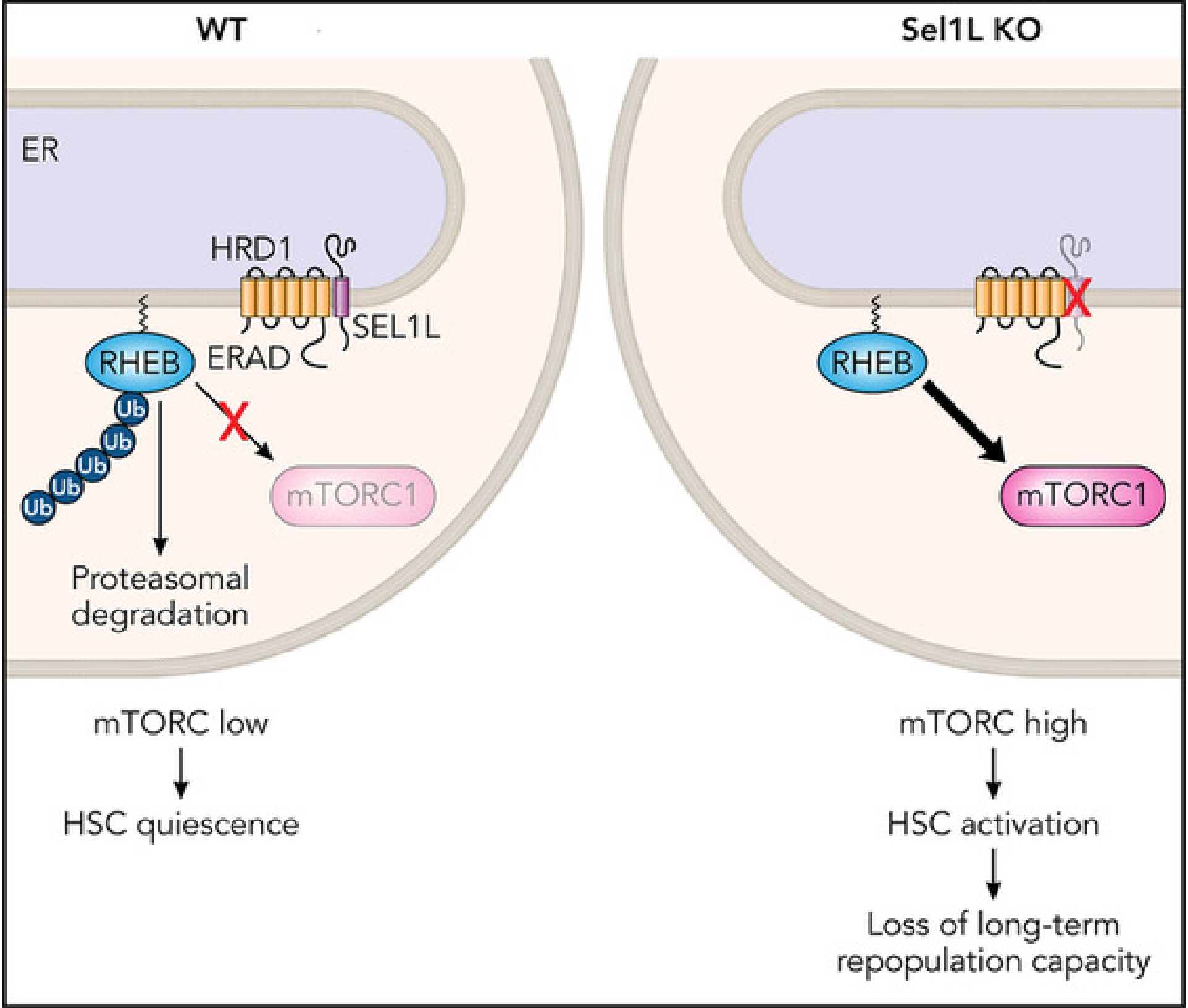
WT
Sel1L KO
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ERAD
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mTORC1
Proteasomal degradation
RHEB
mTORC1
mTORC low
HSC quiescence
mTORC high
HSC activation
Loss of long-term repopulation capacity