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by Vika Miller and Boaz Nachmias

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Proteostasis meets signaling: UBE2G1 in hematopoietic stem cell aging

Vika Miller[1], Boaz Nachmias[1*]

[1] Leukemia Service, Department of Hematology, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel

*Corresponding author:

Boaz Nachmias MD PhD

Head of Leukemia Service, Department of Hematology, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel. BoazN@hadassah.org.il

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Aging of the hematopoietic system is accompanied by progressive loss of stem cell fitness, immune dysfunction, and a sharply increased incidence of clonal hematopoiesis and myeloid malignancies. In this issue of *Haematologica*, *Niemann et al.* identify the E2 ubiquitin-conjugating enzyme UBE2G1 as a novel regulator of age-associated hematopoietic stem cell (HSC) dysfunction[1]. Using genetic and functional approaches, the authors demonstrate that increased UBE2G1 expression is sufficient to induce myeloid skewing, T-cell exhaustion, and impaired thymopoiesis, key hallmarks of hematopoietic aging. Remarkably, these phenotypes are largely independent of UBE2G1's canonical ubiquitin-conjugating activity, instead involving altered phosphorylation signaling and interaction with SHP2. This work establishes a previously unrecognized link between proteostasis regulators and immune aging, with direct implications for age-related myeloid disease.

Protein Homeostasis as a Central Mechanism of Aging

Loss of protein homeostasis (proteostasis) is a defining hallmark of aging. Seminal conceptual work by *López-Otín et al.* placed proteostasis collapse alongside genomic instability and epigenetic drift as a core driver of age-related functional decline across tissues[2]. Proteostasis is maintained through coordinated regulation of protein synthesis, folding, trafficking, and degradation, principally via the ubiquitin-proteasome system (UPS) and autophagy pathways. In the hematopoietic system, proteostasis is particularly critical. *Signer et al.* demonstrated that HSCs require unusually low rates of protein synthesis to preserve self-renewal and long-term function, with even modest increases leading to stem cell exhaustion[3]. More recent work has shown that aged HSCs accumulate misfolded proteins and rely on aggrephagy to maintain viability, underscoring the vulnerability of aging stem cells to proteostatic stress[4]. Together, these studies establish impaired proteostasis as a key intrinsic driver of HSC aging.

The Ubiquitin-Proteasome System and the Role of E2 Enzymes

The UPS is the primary pathway for selective protein degradation and signaling regulation in eukaryotic cells. Ubiquitination is executed through an enzymatic cascade involving E1 activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ligases. While E3 ligases have historically received the most attention due to their role in substrate specificity, it is now clear that E2 enzymes are not merely passive intermediates.

A landmark conceptual synthesis by Stewart and Klevit highlighted that E2 enzymes actively shape ubiquitin chain topology, kinetics, and signaling outcomes, positioning them as regulatory hubs rather than simple “middle men”[5]. This expanded view has important implications for understanding how perturbations in E2 function may influence cellular physiology independently of direct protein degradation. UBE2G1 is a well-characterized E2 enzyme classically associated with K48-linked ubiquitination and proteasomal degradation. Its role has been best defined in the context of targeted protein degradation and therapeutic resistance, including cereblon-dependent pathways in hematologic malignancies[6]. However, its function in normal hematopoiesis and aging biology had not been previously explored. In addition to UBE2G1, other E2 enzymes have been implicated in shaping hematopoietic and immune states that influence clonal selection. Notably, UBE2N (Ubc13), a key mediator of K63-linked ubiquitination and inflammatory signaling, has been shown to regulate hematopoietic stress responses and lineage output[7], supporting the concept that E2 enzymes can actively remodel immune and stem cell fitness landscapes that favor myeloid clonal dominance (Figure 1).

The study by *Niemann et al.* significantly expands the functional landscape of UBE2G1. Using enzyme-dead mutants, the authors show that the aging-associated hematopoietic phenotypes driven by UBE2G1 do not require ubiquitin-conjugating activity. Instead, UBE2G1 alters tyrosine phosphorylation states and interacts with SHP2, a phosphatase with established roles in HSC regulation and leukemogenesis. These findings add to growing evidence that UPS components can exert ubiquitination-independent signaling functions, including scaffolding and modulation of phosphorylation networks. Functionally, increased UBE2G1 expression in young HSCs was sufficient to induce myeloid bias, reduce naïve T-cell output, impair thymic differentiation, and promote expression of exhaustion markers. These phenotypes closely mirror those observed in physiologic hematopoietic aging and suggest that UBE2G1 operates as a molecular accelerator of age-associated immune decline. Notably, these changes occurred in the absence of overt malignant transformation, indicating that UBE2G1 might promote a *pre-leukemic* aging state rather than directly inducing neoplasia. This distinction is critical, as it aligns UBE2G1 with mechanisms that increase susceptibility to clonal selection rather than acting as a classical oncogenic driver.

Aging as a Hallmark of MDS

Age-associated immune skewing, characterized by myeloid bias, reduced lymphoid output, and features of functional exhaustion, is increasingly recognized as a key determinant of hematologic vulnerability in older individuals. Myeloid-biased hematopoietic stem cell (HSC) output not only impairs adaptive immune competence but also expands the pool of long-lived progenitors that are particularly susceptible to cumulative genetic and epigenetic damage. As a result, the aging hematopoietic system adopts an architecture that favors clonal persistence and expansion, creating a permissive environment for clonal hematopoiesis and subsequent progression toward myelodysplastic syndromes (MDS)[8]. Large population-based sequencing studies have demonstrated that age-associated clonal hematopoiesis (CHIP) markedly increases the risk of MDS and acute myeloid leukemia[9]. However, the presence of CHIP mutations alone is insufficient to drive disease, underscoring the importance of the aging hematopoietic microenvironment and intrinsic stem cell dysfunction in shaping clonal fitness[10]. In this setting, immune skewing should be viewed not merely as a consequence of aging but as an active biological process that alters competitive dynamics within the stem cell pool and lowers the threshold for malignant evolution. Within this framework, factors such as UBE2G1 that accelerate immune aging without directly inducing transformation may enhance susceptibility to MDS by reducing the competitive fitness of normal HSCs and reshaping the selective landscape in favor of mutant clones. Accordingly, the findings of *Niemann et al.* position UBE2G1 at the intersection of intrinsic aging biology and disease susceptibility, providing a mechanistic link between immune aging and pre-leukemic risk.

In conclusion, the work by *Niemann et al.* identifies UBE2G1 as a novel regulator of hematopoietic aging, acting through ubiquitination-independent mechanisms that reshape immune and stem cell function. By linking proteostasis, phosphorylation signaling, and age-associated hematopoietic decline, this study provides a conceptual framework for understanding how aging biology predisposes to myeloid disease. As the population ages, integrating aging-related mechanisms into models of MDS pathogenesis will be essential for improving diagnosis, prognostication, and therapeutic intervention.

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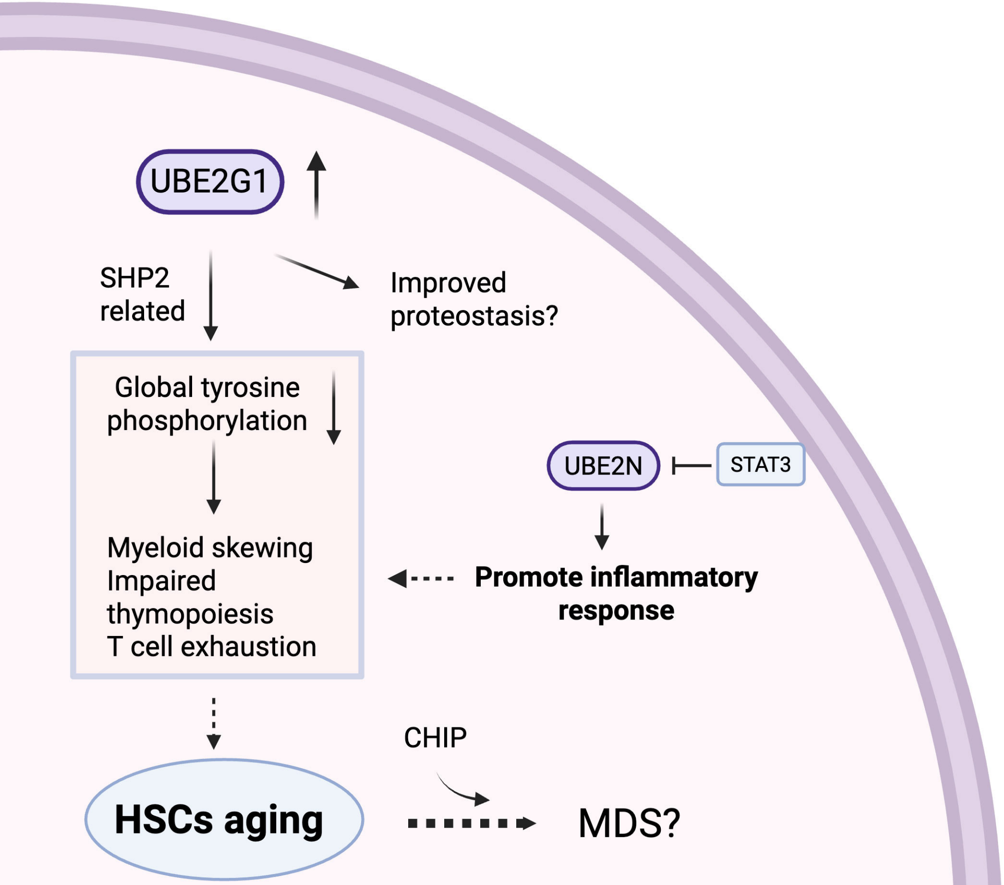
Figure 1. E2 ubiquitin-conjugating enzymes link proteostasis pathways and inflammatory signaling to hematopoietic stem cell (HSC) aging.

Increased expression of UBE2G1 in HSCs engages SHP2 and leads to a global reduction in tyrosine phosphorylation, driving key features of hematopoietic aging, including myeloid skewing, impaired thymopoiesis, and T-cell exhaustion. Although UBE2G1 is a component of the ubiquitin-proteasome system and may, in principle, contribute to protein quality control, the aging-associated phenotypes appear to be mediated predominantly through ubiquitination-independent signaling effects. In parallel, the E2 enzyme UBE2N promotes inflammatory responses, in part through modulation of STAT3-dependent pathways, further reinforcing immune and myeloid skewing. Together, these pathways converge on a state of functional HSC aging, which may create a permissive landscape for clonal hematopoiesis and predisposition to myelodysplastic syndromes (MDS). *Created with BioRender.*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