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Hematopoietic development: a gap in our understanding of inherited bone marrow failure

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Inherited bone marrow failure syndromes (IBMFS) represent a heterogeneous group of multisystem disorders that typically present with cytopenia in early childhood. Efforts to understand the underlying hematopoietic stem cell (HSC) losses have generally focused on postnatal hematopoiesis. However, reflecting the role of many of the involved genes in core cellular functions and the diverse nonhematologic abnormalities seen in patients at birth, studies have begun to explore IBMFS manifestations during fetal development. Here, I consider the current evidence for fetal deficits in the HSC pool and highlight emerging concepts regarding the origins and unique pathophysiology of hematopoietic failure in IBMFS.

Inherited bone marrow failure syndromes (IBMFSs) are multisystem disorders with a predilection for exhaustion of the hematopoietic stem cell (HSC) pool as a near-uniform feature [1,2]. In most patients, symptomatic cytopenias do not manifest until early childhood, but cases of fetal anemia leading to intrauterine hydrops have been reported. Some infants come to attention with constitutional anomalies in other organ systems or through the diagnosis of symptomatic siblings. These seemingly disparate observations are consistent with prenatal HSC defects, even though until recently, few studies had directly pursued this possibility [3,4]. Conversely, many IBMFSs have revealed genetic defects in core cellular functions that can plausibly have an impact on HSC emergence, expansion, or transition between embryonic sites of hematopoiesis. Given the ethical challenges in studying development in humans, the generation of IBMFS model systems has been critical, with mouse and zebrafish models, as well as induced pluripotent stem cells (iPSCs), all providing unique value (Fig. 1).

This article considers the existing evidence for developmental abnormalities in IBMFS hematopoiesis, with emphasis on Fanconi anemia (FA) and Diamond–Blackfan anemia (DBA), as prototypical IBMFSs, along with references to Shwachman–Diamond syndrome (SDS) and the telomere biology disorders (TBDs) where appropriate. Beyond the narrow focus of this article, I highly recommend several excellent reviews discussing IBMFS demographics, pathophysiology, and genetics more broadly [1,5–8].

Hematopoietic manifestations of IBMFSs during development

Given the role of IBMFS genes in core cellular functions, such as DNA repair (FA), ribosome assembly (DBA), and telomere maintenance (TBD) (Table 1), one might reasonably argue that fetal development, with its reliance on highly orchestrated gene expression programs and rapid rates of cell proliferation, is particularly vulnerable to disruption. This notion is consistent with experimental observations. For example, the selective deficiency of ribosomal protein 38 (Rpl38) leads to tissue-specific defects in patterning and organ formation, and investigators observe embryonic lethality after combined loss of aldehyde metabolism and *Fancd2* function [11,35]. These pathways also prove central in maintaining regenerative HSC reserve, which is highly susceptible to altered protein synthesis via changes in ribosome stoichiometry or loss of DNA repair integrity, in DBA and FA, respectively [36,37].

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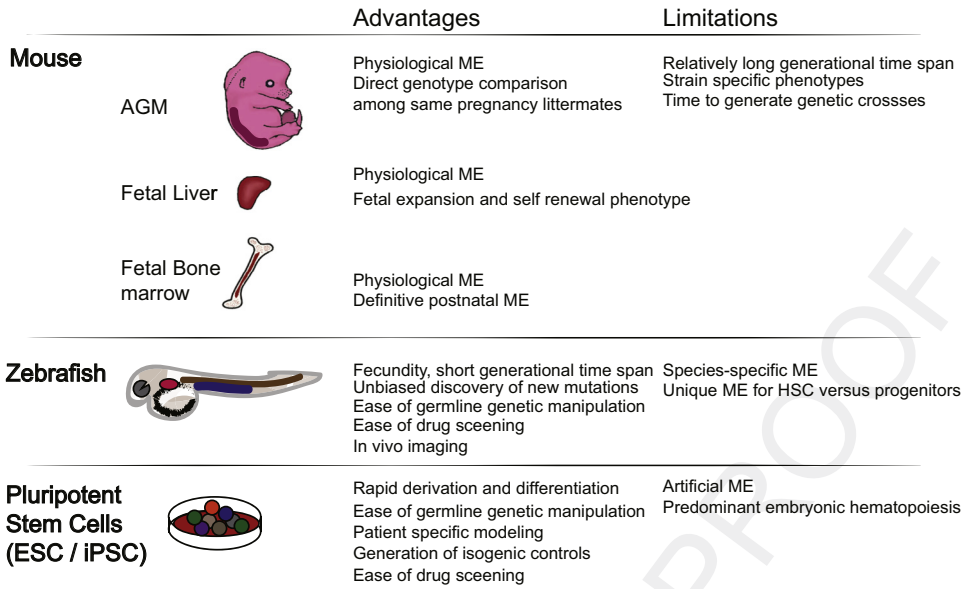

Figure 1. Modeling fetal hematopoietic development. *AGM* = aorto-gonado-mesonephros region; *ESC* = embryonic stem cell; *iPSC* = induced pluripotent stem cell; *ME* = microenvironment.

Clinically, case reports in FA report neonatal cytopenias and reduced cord blood progenitor colony formation [38–40]. Similarly, several instances of fetal anemia in DBA have been reported [41,42]. The pre- or perinatal onset of HSC loss in FA is further supported by the profound $CD34^+$ progenitor deficits in very young patients prior to the onset of severe pancytopenia, as well as observations in human FA fetal liver samples [43,44]. Experimentally, recent studies in several murine models of FA (*Fanc-c, -d2,* and *-g)* revealed losses and functional defects in immunophenotypically defined HSCs from embryonic day (E) 14.5 fetal livers [9,10,17,21]. A mouse model, with transgenic expression of the short form of *Gata1*, a rare variant of DBA, also exhibited significant deficits in erythroid differentiation, compromised fetal liver progenitor colony formation, and early postnatal anemia [45]. Several reports of zebrafish models have linked developmental hematopoietic defects to specific ribosomal protein deficiencies [25,26,46–49]. Finally, studies in embryonic stem cells (ESCs) and patient-derived iPSCs with mutations in FA and DBA genes recapitulate defects in early hematopoietic commitment and specification [12,24,50–53]. Therefore, both clinical observations and experimental data consistently support the developmental onset of hematopoietic failure in several IBMFSs [2,39,40,54].

Available models for the study developmental hematopoiesis in IBMFSs

With the study of human fetal hematopoiesis facing obvious ethical limits, mouse and zebrafish models and patient-derived iPSCs each bring specific strengths to the study of embryonic pathophysiology in IBMFSs (Table 1).

Murine hematopoiesis closely resembles the hierarchical organization in human hematopoiesis, and these models have been invaluable, and arguably imperfect, tools in understanding HSC defects in FA and DBA, but also SDS and TBD [23,55–57]. For example, although the spatial emergence of hematopoiesis in the yolk sac and aorto-gonado-mesonephros (AGM) region seems largely conserved between species, differences in HSC number, cycling activity, clonal dynamics, and telomere regulation have been noted. Compelling insight into other aspects of HSC biology in mice awaits correlation in humans, such as a more refined immunophenotypic definition of HSC or the aging phenotype, as reviewed by Sykes and Scadden [57]. Similarly, there are strong parallels, but also significant gaps in understanding of fetal HSC microenvironments (i.e., AGM, fetal liver, and bone marrow) that may prove important when considering the possibility of non-cell autonomous defects during IBMFS blood development [56,58–61]. Manipulation of the murine germline, breeding, and backcrossing into the desired strain can prove costly, time consuming, and complicated. Moreover, modeling some mutations, such as the haploinsufficiency underlying many ribosome disorders, will require tissue-specific strategies with improved control over temporal and gene dosage regulation [23,27].

Pluripotent stem cells (PSCs) predominantly recapitulate primitive hematopoiesis, but can be induced by canonical Wnt signals to provide definitive hematopoietic output [62]. Validated protocols allow the reprogramming of somatic cells to pluripotency and provide economy in modeling patient-specific mutations with the ability to perform pharmacological screens [12,63–65]. A novel hybrid approach to xenografting iPSC-derived HSPCs into immunodeficient animals may allow in vivo drug screening of human cells [66]. However, the reprogramming process in dyskeratosis congenita (DKC), FA and DBA has not always been straightforward, occasionally