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In Translation

Tipping the Scale: *MYC* Gains Weight in Fanconi Anemia Bone Marrow Failure Progression

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Fanconi anemia (FA) is an inherited syndrome of bone marrow failure (BMF) due to disrupted DNA repair. In this issue of *Cell Stem Cell*, Rodríguez et al. (2021) show that blood stem cells from FA patients have abnormal and inflammation-induced MYC expression, which promotes their proliferation in the face of increasing DNA damage.

Fanconi anemia (FA), the most frequent and genetically heterogeneous inherited bone marrow failure (BMF) syndrome, is caused by biallelic mutations inactivating one of the 23 genes encoding components of the FA/BRCA DNA repair pathway (Rodríguez and D'Andrea, 2017). These mutations can cause downstream DNA damage accumulation and increased chromosome breakage, resulting in BMF. BMF has been attributed to hematopoietic stem cell (HSC) exhaustion and is paradoxically associated with hyperproliferation of hematopoietic stem and progenitor cells (HSPCs) and overactivation of several growth inhibitory pathways, including the p53, TGFβ, and TNFα signaling pathways (Briot et al., 2008; Ceccaldi et al., 2012; Oppezzo et al., 2020; Rosselli et al., 1994; Walter et al., 2015; Zhang et al., 2016).

In this issue of *Cell Stem Cell*, Rodríguez et al. (2021) add insights that resolve this paradox. They demonstrate that the pro-proliferation and pro-survival transcription factor *MYC* is upregulated in HSPCs isolated from the BM of FA patients and that it contributes to the hyperproliferative phenotype of these cells leading to HSPC exhaustion (Figure 1). By taking advantage of recently developed single-cell RNA sequencing methods, they analyze HSPCs isolated from 5 healthy and 7 FA donors and validate *MYC* as one of the top overexpressed genes in all types of progenitors in patient bone marrow. Intra-FA patient variations in *MYC* level appeared to be independent of their age but were inversely correlated with their aplastic status.

The authors then ranked HSPCs according to their intrinsic levels of both *MYC* and *TP53*, which have opposite functions in terms of cell proliferation. This analysis showed that HSPCs in healthy donors contain a clear balanced gradient of expression of *MYC* and *TP53*, an equilibrium which may be important for homeostasis of the hematopoietic system. In contrast, but consistent with the pathological characteristics of their hematopoiesis, this balance is lost in FA patient HSPCs. These cells exhibit more consistent elevations in TP53 levels along with MYC overexpression. This abnormal gradient behavior was present at every stage of HSPC differentiation. Thus, these data fit with the hyperproliferative phenotype of FA HSPCs (*MYC* overexpression) as well as their exhaustion (*TP53* overexpression).

Although the study is limited in terms of the number of patients analyzed, Rodríguez et al. extended their initial observations by validating overexpression of *MYC* and MYC targets *in vitro*, in an FA cell line mutated for *FANCG* and by shRNA knockdown of FANCD2 in human CD34+ cord blood cells, and *in vivo* in a Fancd2$^{-/-}$ mouse model. As a further link between dysregulated MYC expression and BMF in FA, they show in Fancd2$^{-/-}$ mice that inhibiting Myc transcription with the BRD4 inhibitor (+)-JQ1 decreases the proliferative capacity of HSPCs and that this is associated with lower levels of DNA damage. Taken together, these results suggest that abnormal *MYC* upregulation sustains HSPC proliferation and survival, despite accumulation of DNA damage, while also impeding quiescence to repair that damage.

Mechanistically, the authors propose that *MYC* overexpression promotes entry into the cell cycle by promoting both speed and firing of replication forks.

What are the origins of the *MYC* overexpression in FA HSPCs? It has been known for decades that FA cells overexpress a large number of pro-inflammatory cytokines as TNFα (Rosselli et al., 1994). Treatment of WT mice with the pro-inflammatory double-stranded RNA mimetic pI:pC only slightly increases *Myc* expression. However, similar treatment strongly elevates *Myc* expression in the HSPCs from FA mice and significantly alters their numbers. Consistently, plasma from FA patients shows significant increases in levels of circulating pro-inflammatory cytokines MCP-1 and TNFα compared to healthy donors. Validating the importance of pro-inflammatory cytokines, the authors show that exposure to pro-inflammatory cytokines IFNγ or TNFα is per se sufficient to induce *Myc* overexpression in FA mice and FANCA mutant CD34+ cord blood cells. Notably, all of these effects can be reversed by (+)-JQ1.

Finally, the authors suggest that *MYC* overexpression participates not only in maintaining HSPCs in a proliferative status but also contributes to their exit from the bone marrow niche. They find by differential gene expression analysis that FA *MYC* overexpressing cells downregulate several genes encoding adhesion proteins, including CXCR4 and Vimentin,

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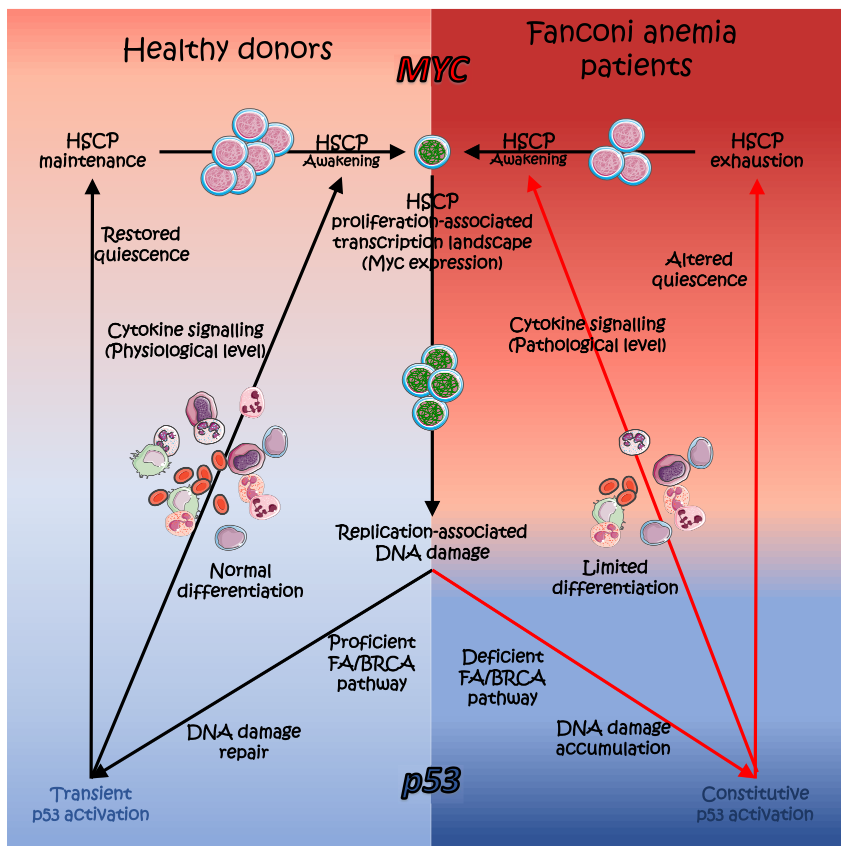

Figure 1. Balancing MYC and p53 Activity in HSPCs from Healthy Donors and FA Patients
Rodríguez et al. (2021) detail a continuum of p53 and MYC expression in HSPCs from healthy donors, which is disrupted in cells obtained from FA patients. Elevated MYC activity in these cells promotes HSPC hyperproliferation despite accumulation of DNA damage and p53 activation, which is itself a hallmark of FA-associated HSPC exhaustion.

critical factors involved in HSC adhesion to their bone marrow niche. Accordingly, the peripheral blood of FA patients contains more circulating primitive CD34+ cells with even higher MYC levels compared to BM CD34+ cells, suggesting that weaker adhesion to their niche contributes to HSPC exhaustion in FA.

In summary, the study by Rodríguez et al. provides important new insights into the origins of BMF in FA and the complexity of this rare and paradigmatic genetic syndrome. Moreover, it raises important new questions. What are the pathways and mechanisms linking pro-inflammatory cytokines to the increased transcription of *MYC* in FA HSPCs? What is the first signal that leads to pro-inflammatory cytokine overexpression? Is it just the initial response to physiological demands of maintaining normal blood cells and platelet counts? Or does the FA/BRCA pathway have direct functions in cytokine expression and signaling (Ma et al., 2009)? Is it just an indirect consequence of DNA damage and DNA accumulation in cytoplasm (Brégnard et al., 2016)? How MYC-dependent transcriptomic landscapes participate in the replication fork regulation likewise remains to be elucidated. Interestingly, MYC belongs to the same family of transcription factors as MiTF, which is highly expressed in FA HSPCs (Oppezzo et al., 2020). It would be interesting to see not only how MiTF behaves in the reported gradient but also if it changes in response to (+)-JQ1. While it will be challenging to develop MYC inhibitors for treating BMF in FA patients, these results suggest potential routes for therapeutic interventions in these patients.

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