calcium consumption does not seem to have such an effect. How to optimize calcium supplements for human health deserves further investigation.

Maybe it's time to determine whether low-fat milk–based drinks taken as an alternative to the soda so frequently consumed, especially during the early adolescent years, can attain the noble goal of keeping bones healthy—without increasing the risk of coronary heart disease, which has been associated with calcium supplementation[13].

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IFN-α wakes up sleeping hematopoietic stem cells

Emmanuelle Passegué & Patricia Ernst

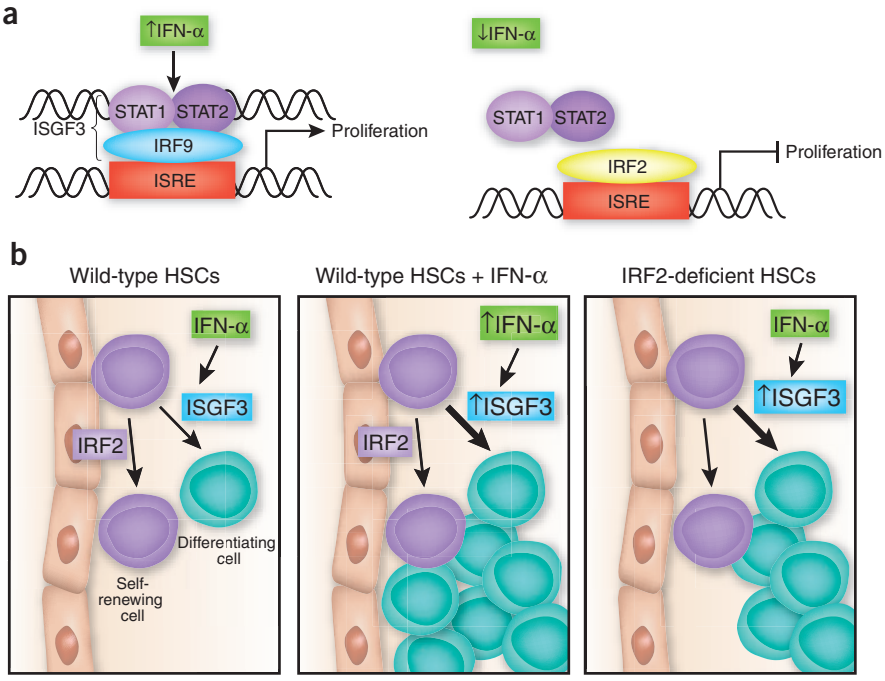
The cytokine interferon-α stimulates the turnover and proliferation of hematopoietic cells *in vivo* (pages 696–700). The findings hint at a new strategy to treat hematopoietic cancers.

At homeostasis, complex regulatory networks maintain the ongoing production of all blood cell types[1]. During this process, very few hematopoietic stem cells (HSCs) actively divide, and most of them remain quiescent in the bone marrow. In response to injury to the hematopoietic system, such as from irradiation or chemotherapy, HSCs can temporarily exit their quiescent state and generate a larger pool of progenitor cells, thus increasing production of the needed mature blood cells. Some of the proteins that regulate the choice between quiescence and proliferation in HSCs have already been identified[1,2].

Two recent studies, one in *Nature*[3] and the other in this issue of *Nature Medicine*[4], now expand upon this small list of players. The studies show that the cytokine interferon-α (IFN-α) stimulates the turnover and proliferation of HSCs *in vivo*[3,4]. IFN-α is an important immune modulator not previously known to influence HSC function. This feedback mechanism between the immune system and the tip of the hematopoietic hierarchy may lead to a new strategy for leukemia treatment.

Type I interferons (IFN-α and IFN-β) are produced by a variety of immune and nonimmune cells in response to microbial infections or recognition of tumor cells[5]. Upon engaging their receptors, type I interferons induce a set of genes that inhibit viral replication and clear infected cells. Because of their ability to regulate the immune system, recombinant type I interferons have been used clinically to treat viral infections, solid tumors, myeloproliferative disorders, hematopoietic neoplasms and autoimmune diseases such as multiple sclerosis. For most of these diseases, the mechanisms of action and the precise cellular targets of IFNs are still largely unknown, but IFN-α treatment of cancer cells generally results in growth arrest by activating negative regulators of proliferation such as p53 (ref. 6).

Now Essers *et al.*[3] and Sato *et al.*[4] report a new role for IFN signaling within the most primitive cells of the hematopoietic system. The two groups came to similar conclusions starting from very different observations. In



Kim Caesar

Figure 1 Role of low-level and induced IFNα signaling within HSCs. (**a**) Hypothetical target gene linking IFN-α signaling to HSC proliferation. Left, IFN-α–induced proliferation via the ISGF3 complex; right, endogenous (uninduced) IFN-α signaling, in which IRF2 acts on the same hypothetical gene to constitutively suppress expression. ISRE, IFN-stimulated response element. (**b**) Outcome of HSC proliferation in the presence of endogenous IFN-α signaling, induced IFN-α signaling (↑IFN-α) and in the IRF2 knockout. Arrows indicate decisions of the stem cell to divide to yield mostly progeny committing to differentiate (blue-green cells) versus dividing to self-renew and maintain the stem cell pool (purple cells).

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the course of using a mouse model commonly employed in the study of HSC function, Essers *et al.*[3] found that high levels of IFN-α induced HSC proliferation. Sato *et al.*[4] were studying the immune modulatory effects of IFNs and other cytokines on immune effector cells when they found that mice lacking a component of the IFN signaling pathway had an unexpected imbalance of proliferation within the HSC pool. Both groups tracked their observations to a direct effect of IFN-α on the proliferation state of HSCs[3,4].

Sato *et al.*[4] studied mice that were genetically deficient for a negative regulator of type I interferon signaling, interferon response factor-2 (IRF2)[4,7]. The investigators discovered that these mice had a greater proportion of HSCs that were proliferating, instead of quiescent as would be found in normal mice. Chronic proliferation can impair certain functions of HSCs, such as their ability to repopulate the bone marrow of irradiated mice[2]. Sato *et al.*[4] found that the IRF2-deficient HSCs were unable to restore hematopoiesis in irradiated mice, indicating that this cell population was no longer fully functional. However, if type I IFN signaling was disabled in the HSCs, the ability to repopulate the bone marrow could be restored in IRF2-deficient HSCs. This observation suggests that IRF2 normally suppresses IFN signaling in wild-type HSCs, maintaining these cells mostly in a dormant state (**Fig. 1**).

Both groups found that high levels of IFN-α directly induced wild-type HSCs to exit quiescence and transiently proliferate *in vivo*[3,4]. Because most cell types stop proliferating in response to IFN-α[5], the wiring of this signaling pathway must be fundamentally different in HSCs. Signaling by type I IFNs activates a complex called interferon-stimulated gene factor-3 (ISGF3), which is composed of signal transducer and activator of transcription-1 (STAT-1), STAT2 and IRF9 (**Fig. 1**). IRF2 lacks the domain required for Stat protein interaction and so interferes with IFN signaling and IRF9-mediated transcription. Essers *et al.*[3] found that Stat1 was required for the IFN-α–mediated exit from dormancy, indicating that this unusual effect on proliferation is mediated by a canonical IFN signaling component. How IFN-α signals are interpreted differently in HSCs compared to other cell types is yet to be determined.

A remaining mystery is why an important antiviral signal should influence HSC activity and hematopoiesis. The induced proliferation of HSCs could be a means to replace the immune cells turned over in the process of viral clearance. However, both groups show that one outcome of the enhanced HSC proliferation is ultimately the decreased production of mature cells[3,4]. So it is unlikely that this feedback mechanism is in place simply to amplify cells at the top of the hematopoietic hierarchy. One aspect not investigated by either group is whether the proliferating HSCs are mobilized or trafficked differently as compared to noninduced HSCs. Previous studies have illustrated that bacterial products mimicking infection cause the preferential migration of HSCs into peripheral tissues, where they participate in immune regulation by differentiating into immune effector cells[8]. Therefore, the HSC proliferation induced by IFNs may serve to generate immune effector cells from circulating HSCs for rapid deployment against infections or tumor cells.

In contrast to the value of this feedback system to the hematopoietic system, the potential clinical value of these findings is quite clear. IFN-α has long been used as a therapy for cancer, particularly for chronic myelogenous leukemia (CML), owing to its growth inhibitory and immune modulatory activities. The discovery of the proliferative effect of IFN-α on quiescent HSCs provides an exciting new interpretation for recent data from human subjects[9,10]. Strikingly, a handful of CML patients that were first treated with IFN-α and then switched to imatinib treatment—a molecularly targeted therapy directed against BCR-ABL, the fusion protein characteristic of CML—experienced persistent remission, and perhaps cure, upon drug discontinuation[9,10]. In contrast, patients from the same study, and from other clinical cohorts, who achieved remission after imatinib treatment but were not previously treated with IFN-α, often relapsed upon imatinib discontinuation[9–11]. Persistent CML-initiating cells, or CML stem cells, which are protected from imatinib killing by their quiescent status, are probably responsible for the regrowth of the disease[12].

The emerging possibility to explain the stable remission in the patients previously treated with IFN-α could be that the exposure to IFN-α induced the CML stem cells to exit quiescence and proliferate such that, upon imatinib treatment, they became vulnerable to imatinib rather than remaining protected.

Although the results of the patient studies need to be confirmed in larger studies, they raise the tantalizing possibility of an effective targeting strategy for drug-resistant quiescent cancer stem cells in individuals suffering from CML and other hematologic malignancies[11]. These new insights into the role of IFN signaling in normal HSC quiescence may spark further interest in manipulating this pathway to kick quiescent leukemia stem cells into a more vulnerable state.

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