Type I interferons: leukemia's old foe in the limelight again

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In this issue of *Haematologica*, Smeets *et al.*[1] shed new light on the regulation of the classical immunomodulatory cytokine family, type I interferons (IFN-I), in the *ETV6-RUNX1* subgroup of acute lymphoblastic leukemia (ALL). Discovered in 1957 by Isaacs and Lindenmann, IFN-I gained prominence as critical regulators of antiviral innate immune responses. IFN-I production in response to viral infection or DNA damage induces the expression of IFN-stimulated genes (ISG). These ISG mediate the anti-proliferative, pro-apoptotic, and pro-inflammatory functions of IFN-I, a process that ultimately results in the elimination of the infected and/or damaged cells either directly or by host immune cells.[2] Immune responses in cancers mimic those seen during viral infections.[2] Consistent with this, Dunn and colleagues made the landmark discovery that IFN-I restrict solid tumorigenesis by activating both innate and adaptive arms of anticancer host immune defenses.[3] IFN-I are thus widely regarded as 'anticancer' cytokines.

IFN-α2, a member of the IFN-I family, was the first immunotherapeutic agent to be approved by the US Food and Drug Administration in 1986 for the treatment of hairy cell leukemia.[4] The remarkable response rates observed in patients with hairy cell leukemia led to the expanded use of this cytokine in the treatment of other hematopoietic malignancies, including ALL.[5] In ALL, IFN-I were shown to increase relapse-free survival in patients who received an allogeneic bone marrow hematopoietic stem cell transplant.[5] Despite the remarkable improvements in clinical outcomes of patients treated with IFN-I, IFN-I gradually lost their charm as 'wonder drugs' due to off-target toxicity associated with their administration.[2] Nevertheless, their strong anticancer function could never be refuted. IFN-I were unfortunately used in clinics at a time when their mode of therapeutic action was not completely understood. However, recently identified mechanisms of action of IFN-I in human ALL by Smeets *et al.*[1] and us[6] rekindle the interest of the scientific community in harnessing the therapeutic potential of this age-old cytokine family in treating ALL.

In 2005, Einav *et al.*[7] discovered that patients with the most common and treatable form of childhood B-cell precursor (BCP) ALL, the *ETV6-RUNX1*$^+$ subtype, were approximately three times more likely to exhibit an enhanced expression of ISG in comparison to children with high-risk BCP ALL subtypes such as those with *MLL*, *E2A-PBX1*, or *BCR-ABL1* rearrangements and hypodiploidy. However, they did not delve into why *ETV6-RUNX1* BCP ALL were associated with interferonopathy, which cells in the leukemia microenvironment cause such interferonopathy, and which class(es) of IFN were induced.

In the current issue of *Haematologica*, Smeets *et al.*[1] answer some questions arising from the publication by Einav and colleagues.[7] They found that in pediatric patients with BCP ALL, bone marrow mesenchymal stromal cells (MSC) are a critical source of interferons, specifically the IFN-I α and β. Among childhood BCP ALL subtypes, they found that *ETV6-RUNX1*$^+$ ALL most profoundly induces ISG in co-cultured bone marrow MSC derived from healthy donors and from children with *ETV6-RUNX1*$^+$ and other ALL (hyperdiploid and those with *DUX4*, *CRLF2*, and *EPOR* translocations). They show that induction of ISG in MSC co-cultured with *ETV6-RUNX1*$^+$ ALL cells occurs partly by direct contact between leukemic cells and MSC via tunneling nanotubes (Figure 1). Overall, the findings of Smeets and colleagues suggest that ETV6-RUNX1 could be a direct inducer of the IFN-I pathway in normal and ALL patient-derived MSC. Mechanistically how expression of ETV6-RUNX1 in leukemic blasts triggers the IFN-I signature in surrounding non-malignant MSC remains to be delineated. Together, the studies by Einav *et al*. and Smeets *et al*. raise interest in studying these biological mechanism(s).

Smeets and colleagues also observed that IFN-I from MSC co-cultured with *ETV6-RUNX1*$^+$ BCP ALL cells do not directly impact the viability of the leukemic cells or their sensitivity to chemotherapeutic agents.[1] This observation

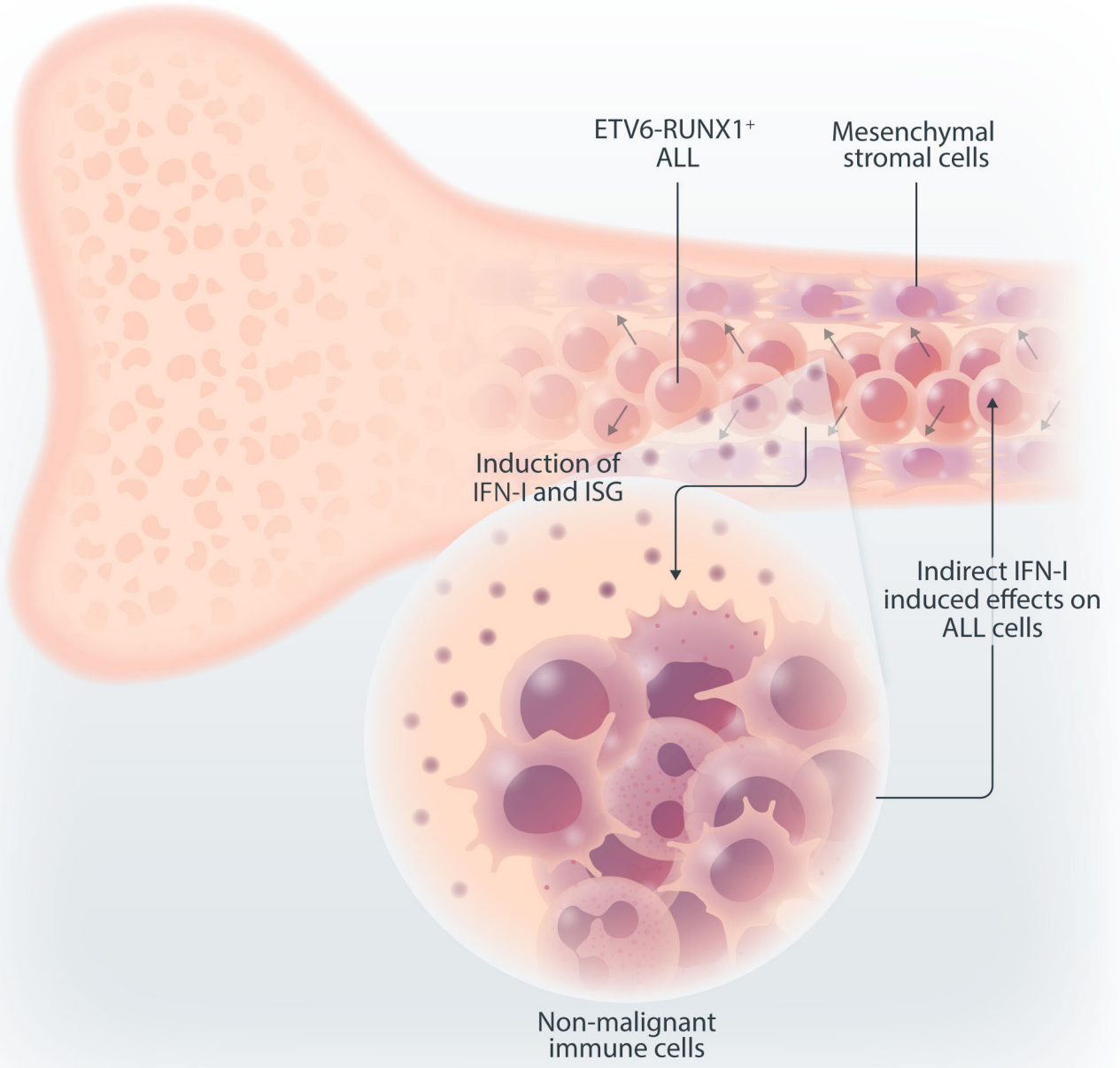

Figure 1. Type I interferons in B-cell precursor acute lymphoblastic leukemia. Smeets *et al.* found that acute lymphoblastic leukemia (ALL) cells, primarily the *ETV6-RUNX1*+ subtype, induce the paracrine expression of type I interferons (IFN-I) and IFN-I-stimulated genes (ISG) in co-cultured bone marrow mesenchymal stromal cells (MSC). IFN-I pathway induction in MSC is partially mediated via direct contact between leukemia cells and MSC. Induction of ISG and IFN-I production from MSC has an indirect effect on the ALL. This indirect effect of MSC-derived IFN-I may be potentially mediated by non-malignant host immune cells.

is consistent with Dunn *et al*.'s seminal finding that only cells of the hematopoietic lineage mediate the anticancer effects of IFN-I. Dunn *et al*. made their discovery in a solid tumor model of fibrosarcoma that is very different from leukemia in which malignancy arises in the hematopoietic cells themselves.[3] Studying the role of IFN-I in BCP ALL, we showed that IFN-I mediate their anti-leukemic effects indirectly by activating host immune defenses. We found that IFN-I enhance the production and maturation of the non-malignant, innate immune cytotoxic natural killer cells in the ALL microenvironment by stimulating the production of interleukin-15, the IFN-I-induced cytokine critical for natural killer-cell homeostasis.[6] We found significantly higher expression of interleukin-15 in patients with *ETV6-RUNX1*+ BCP ALL than in higher risk ALL subgroups, suggesting more intact IFN-I-induced immune responses in the former.[6] The work by Smeets *et al.* thus complements ours by demonstrating that: (i) MSC-derived IFN-I mediate their effects on ALL indirectly; and (ii) *ETV6-RUNX1*+ BCP ALL have a distinctly higher IFN-I-driven immune response signature in comparison to other ALL subtypes (Figure 1).

The publication by Smeets and colleagues is topical and opens additional avenues for research. The *ETV6-RUNX1* subgroup of BCP ALL is unique in terms of its clinical outcome and etiology. Children with this form of ALL have one of the most favorable clinical outcomes with event-free survival for these patients after standard therapies exceeding 90%.[8] The increased IFN-I pathway signature in ETV6-RUNX1-driven BCP ALL as compared to other ALL subtypes and the heightened ability of *ETV6-RUNX1*+ ALL cells to induce ISG in surrounding MSC[1] could explain the favorable clinical outcomes of patients with this form of ALL. Another interesting feature of *ETV6-RUNX1*+ BCP ALL

is that not all individuals who acquire this translocation *in utero* go on to develop overt leukemia.[9] The extent of IFN-I-mediated antileukemic responses by MSC may determine the risk of development of overt leukemia in individuals born with the *ETV6::RUNX1* rearrangement.[10] The above theories require experimental testing. Lessons learnt from the role of IFN-I in *ETV6-RUNX1*$^+$ ALL will also inform the development of safer therapeutic alternatives to direct IFN-I administration for treating higher risk BCP ALL subgroups.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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