INTERFERing T-ALL progression: a multifaceted therapy

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In this issue of Haematologica, a new manuscript by Goosens et al(1) elegantly dissects the direct and indirect therapeutic effects of type-I interferons (IFN-I) in the treatment of T-cell Acute Lymphoblastic Leukemia (T-ALL). Even if advances in T-ALL treatment in the last decades have resulted in high cure rates, 20-50% of cases still relapse and ultimately die, underscoring the need to identify novel therapeutic strategies and to properly stratify patients that might respond to specific targeted agents(2). Interferons have been widely used in the treatment of both solid and hematological tumors due to their multiple anticancer properties, which include direct cancer cell-intrinsic cytostatic/cytotoxic effects, as well as immune system-mediated cancer cell-extrinsic effects(3). However, IFN-I therapy in cancer has typically resulted in uneven and unreliable results given their poor anticancer properties in some tumors together with complex side effects due to their pleiotropic activity(4).

In order to assess the direct anticancer activity of IFN-I in T-ALL, Goossens and colleagues treated different human T-ALL cell lines as well as T-ALL patient-derived xenografts (PDXs) with human IFN-I, both in vitro and in vivo. Consistent with previous literature(5), the
antileukemic effects of IFN-I stimulation were only observed in samples that showed JAK/STAT1 activation upon treatment with IFN-I, as measured by pSTAT1 intracellular staining. These results suggest that this fast and easy method to analyze pSTAT1 levels in patient cells in vitro could be used as a biomarker to stratify patients that might respond to IFN-I treatment.

In order to assess the indirect anticancer effects of IFN-I in T-ALL, authors then used a model of PTEN-null and IFN-I-sensitive mouse primary leukemia, upon transplantation into both immunocompetent or immunodeficient recipients. These experiments showed that, even if murine IFN-I treatment resulted in antileukemic effects with extended survival in both settings, its therapeutic effects were much stronger in the presence of an intact immune system, demonstrating its significant immune-mediated cell-extrinsic antileukemic effects. Next, authors used Activity-on-Target interferons (AcTaferons; AFN)(6) in order to specifically direct the activity of IFN-I to CD8-positive murine cells (mCD8-AFN), given that roughly half of T-ALLs are CD8-positive and, moreover, CD8 is also expressed by mouse classical dendritic cells type I (cDC1), which are relevant for triggering a CD8 cytotoxic response (CTL) upon IFN-I stimulation(7). In this context, as expected, mCD8-AFN treatment in immunodeficient mice resulted in antileukemic effects only when these mice harbored CD8-positive, not CD8-negative, mouse leukemias. However, rather unexpectedly, similar results were also obtained when these CD8-positive or CD8-negative were transplanted into immunocompetent mice. By contrast, when authors used a different AcTaferon directed to Clec9a (mClec9a-AFN), which has been shown to elicit a cDC1-mediated anti-tumor response in other tumors(7), significant antileukemic effects were observed in vivo in immunocompetent mice harboring both CD8-positive or CD8-negative leukemias. Importantly, mClec9a treatment even resulted in 20-40%
cure rates, while no leukemic mouse was cured either by mCD8-AFN or mIFN treatment itself. Interestingly, and as expected (given that Clec9a is not expressed in normal or malignant T-cells), this antileukemic effect was completely absent if these leukemias were transplanted in immunodeficient mice, highlighting that mClec9a-AFN antileukemic effects are driven exclusively by immune system-mediated anti-tumor responses.

These results showing strong indirect effects for mClec9a-AFN but reduced/absent for mCD8-AFN are intriguing. Previous studies showed that IFN signaling in DCs, not T-cells, is required for AFNs antitumor activity, however, optimal antitumor effects of AFNs are still dependent on the presence of CD8-positive cytotoxic T-cells (CTLs)(8), and priming and activation of CTLs requires prior activation and maturation of DCs. One possibility to explain these discordant results might be that binding of the mCD8-AFN on CTLs could neutralize their cytotoxic properties, however, this is unlikely since mCD8-AFN was previously shown to have significant additive antitumor effect in combination with TNF-based targeted therapy(9). Moreover, in the current Haematologica manuscript, mCD8-AFN treatment seemed to translate into improved antileukemic effects in CD8-positive leukemias transplanted into immunocompetent mice, as compared to immunocompromised mice. Another interesting but bizarre possibility to reconcile these results might be that, in order to elicit its indirect immune-mediated effects, mCD8-AFN treatment might first require some direct cell-intrinsic effects to take place, which would thus explain indirect effects being observed only on CD8-positive leukemias. Finally, it is also possible that mCD8-AFN does not activate cDC1 cells to the same extent as mClec9a-AFN, or that a different Clec9a-positive hematological population might be more relevant in order to mediate the therapeutic effects observed. Related to this, it would be interesting to test the potential synergistic effects of mCD8-AFN and mClec9a-AFN when used concomitantly to treat
CD8-positive leukemias. Further research is therefore warranted to uncover the biological reasons for these differences. Regardless, the important findings by Goossens and colleagues serve to revitalize the field of interferons for the treatment of T-cell malignancies, as AFNs show significantly reduced side effects as compared to IFN itself, and both mCD8-AFN and mClec9a-AFN showed direct and/or indirect antileukemic properties which could be exploited for the treatment of IFN sensitive-leukemias alone or in combination with classical chemotherapy regimens which, in turn, might help reduce or prevent relapses in these patients.

**Disclosures**

No conflicts of interest to disclose.

**References**


