Teaching an old dog new tricks: Activity-on-Target Interferon to treat T-cell acute lymphoblastic leukemia

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INTRODUCTION

Type I interferon (IFN) has a long history in the treatment of cancer, including hematological malignancies. The anti-cancer effects induced by IFN result from a combination of 1) direct cancer cell growth inhibition by cell cycle arrest, apoptosis, or differentiation and 2) the activation of the immune system involving antigen presentation by Clec9A+ dendritic cells and priming of cytotoxic CD8+ T-cells. However, IFN therapy experienced variable and unpredictable success in the clinic. Its clinical application is severely impeded by a complex pattern of adverse side-effects, due to the multifaceted activity pattern of IFN.

Therefore, safe exploitation of the anti-cancer potential of IFN requires strategies to direct their activity to selected target cells, avoiding systemic toxicity.

OBJECTIVE AND METHODS

Safe exploitation of the anti-cancer potential of IFN requires strategies to direct their activity to selected target cells, avoiding systemic toxicity.

To improve the therapeutic index of IFN, we have developed Actaferons (Activity-on-Target Interferon), optimized (mutant) immunocytokines. Mutated IFNα2bQ124A, with a strongly reduced affinity for its receptor complex, was fused to single domain antibodies targeting cell-specific domains, which selectively restores the Actaferon (AFN) activity in a cell-type specific manner. As such, mCD8-AFN and mClec9A-AFN were generated which selectively target either mouse CD8+ T-ALL cells or Clec9A+ dendritic cells.

To test the anti-leukemic properties of these Actaferons we generated syngeneic T-ALL cell lines:

The specificity of the Actaferons was evaluated in vitro:

mCDB-AFN has direct anti-leukemic properties

mCDB-AFN treatment after T-ALL transplantation in immunocompromised mice (NSG):

AFNs have less adverse side-effects

Adverse side-effects were evaluated in leukemia-free mice in comparison to wildtype interferon

CONCLUSIONS

• Activity-on-Target Interferons (Actaferons; AFN) were generated with selective activity on CD8+ and Clec9A+ cells.
• mouse CD8-Actaferon (CDB-AFN) induces a direct and highly selective anti-proliferative/leukemic effect only on CD8+ acute T-cell lymphoblastic leukemia (T-ALL) cells; both in vitro and in vivo.
• mouse Clec9A-Actaferon (mClec9A-AFN) induces an indirect anti-leukemic effect on mouse T-ALLs by activation of the immune system.
• Due to the selective cell targeting, a drastic reduction in toxic side-effects was observed with Actaferons compared to the treatments with the wild type IFN.

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