Targeting SIRPα in cancer

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Strategies to harness the patient’s immune system to fight cancer have mainly involved adoptive T-cell transfer. We and others have recently highlighted an alternative immunotherapeutic approach to cancer that consists in enhancing the macrophage-mediated clearance of leukemic cells through the blockade of inhibitory signals transmitted by signal regulatory protein α (SIRPα).

Despite decades of clinical trials, the prognosis of patients with acute myeloid leukemia (AML) remains poor and many of them experience recurrent disease. One factor contributing to the high relapse rate of AML patients is the intrinsic resistance of leukemia stem cells (LSC) to standard chemotherapy. Hence, research is currently focused on the development of novel anti-leukemic agents that better target these disease-sustaining cells. However, it has recently been shown that leukemias are composed of genetically and functionally diverse subclones,1,2 predicting that LSC-directed therapeutics may not eradicate the disease when distinct LSC subclones are not equally dependent on the drugged pathway. The recognition of both intratumoral and inter-patient heterogeneity in leukemia has also led to a greater use of primary patient samples, as opposed to cell lines, for drug development, as the latter cannot capture the heterogeneity of therapeutic responses that is frequently seen in the clinic. The efficacy of candidate anticancer agents against LSCs can be tested by treating immunodeficient mice bearing human leukemic grafts in xenotransplantation assays, with the hope that observed drug responses will predict responses in patients.

These aspects of anticancer drug development converged in our recent study showing that LSCs in AML rely on signal regulatory protein α (SIRPα) signaling to evade immune surveillance by macrophages in xenotransplantation assays.3 This work builds on our previous demonstration that the binding of SIRPα on mouse macrophages to its ligand CD47 on normal human hematopoietic stem cells (HSCs) generates an inhibitory signal that prevents phagocytosis and allows for hematopoietic engraftment in xenotransplant recipients.4 Since HSCs and LSCs share many biological properties, we used the genetic tools that we had previously developed, i.e., mouse strains congenic for Sirpα variants that confer differential binding to human CD47 (hCD47) as well as a novel human SIRPα (hSIRPα)-Fc fusion protein, to show that SIRPα-mediated inhibition of macrophages is also required for LSC survival following AML cell xenotransplantation, suggesting that targeting this interaction may promote antitumor immunity.

CD47 has long been known to act as a “marker of self” on red blood cells5 and platelets6, regulating their timely clearance by macrophages. It is therefore not surprising that cancer cells have exploited this mechanism of self-recognition to evade immunosurveillance (Fig. 1). In line with this notion, elevated expression levels of CD47 constitute an adverse prognostic factor for AML patients.7 Our studies demonstrate that the disruption of SIRPα-CD47 interactions with a hSIRPα-Fc fusion protein results in the preferential phagocytosis of AML cells over normal human hematopoietic cells. These findings indicate that pro-phagocytic signals evoked by AML cells are more robust than those elicited by normal cells, targeting the former for elimination when SIRPα inhibitory signals are blocked. Thus, leukemic cells rely more heavily on SIRPα engagement to evade phagocytic clearance by macrophages. This notion creates a therapeutic opening for agents that disrupt SIRPα-CD47 interactions, which may allow for the preferential clearance of leukemic cells over their normal counterparts.

Therapeutic approaches that enable host antitumor immune responses, such as the blockade of SIRPα-CD47 interactions, potentially circumvent the problem of resistance to LSC-targeted therapies that may result from subclonal diversity. Agents that disrupt SIRPα-CD47 interactions may also synergize with therapeutic monoclonal antibody therapies that promote the Fc-receptor-mediated clearance of targeted cells.8,9 Indeed, anti-CD47 antibodies as well as the hSIRPα-Fc fusion protein may also act, at least in part, by activating antibody-dependent...
cell-mediated cytotoxicity. Recently, an alternative strategy to enhance antitumor immunity has been reported. In this setting, agonist anti-CD40 antibodies were shown to re-educate tumor-associated macrophages (TAMs) and induce tumor regression in a mouse model of pancreatic cancer. This study highlights the complex roles of macrophages in tumor biology: as opposed to classically activated macrophages, which mediate tumor surveillance, TAMs have been implicated in the progression of both solid and hematologic malignancies, owing to their multipronged tumor-supportive functions. Recent evidence indicates that macrophages form part of the normal HSC bone marrow niche, raising the intriguing possibility that a subset of these cells may support the survival of LSCs. Ultimately, a better understanding of these complex processes and the role that SIRPα plays in this setting will promote the development of novel therapeutic agents that specifically modulate these interactions.

The identification of SIRPα as the key CD47 binding partner involved in the inhibition of the macrophagic clearance of leukemia cells paves the way for strategies to disrupt SIRPα-CD47 interactions via the direct targeting of SIRPα on immune cells, rather than CD47 on tumor cells. Due to the relatively restricted tissue expression pattern of SIRPα, SIRPα antagonists may be better tolerated than agents targeting CD47 on tumor cells. Due to the relatively restricted tissue expression pattern of SIRPα, SIRPα antagonists may be better tolerated than agents targeting CD47, which is ubiquitously expressed, binds to multiple other ligands, including integrins and thrombospondin, and governs several processes in both normal and malignant tissues. To maximize their utility to enhance antitumor immunity, SIRPα antagonists must block the interaction of CD47 with SIRPα while minimizing SIRPα signaling. Antagonist anti-mouse and human SIRPα antibodies have been described. Future work is needed to determine whether humanized anti-SIRPα antibodies or other SIRPα antagonists can be developed for clinical use.

Disclosure of Potential Conflicts of Interest
There is an existing license agreement between Trillium Therapeutics Inc. and UHN/SickKids Hospital, and J.S.D. and J.C.Y.W. may be entitled to receive financial benefits further to this license and in accordance with their respective institutions’ intellectual property policies. The authors have no additional financial interests.

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