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Comment on Laouedj et al, page 1980

S100 proteins in AML: differentiation and beyond

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In this issue of Blood, Laouedj and colleagues make a new and important contribution to our understanding of cell differentiation impairment in acute myeloid leukemia (AML) by illuminating the role of S100 proteins and Toll-like receptor (TLR) signaling.1 Although differentiation blockade has been recognized as a hallmark of AML for decades, direct therapeutic application of this concept has been limited to only a subtype of AML, acute promyelocytic leukemia (APL), in which the PML-RARA fusion protein is targeted by the differentiating agents retinoic acid and arsenic trioxide.2 The extraordinary clinical outcomes achieved by this strategy in APL have motivated efforts to pharmacologically release the differentiation block in other AML subtypes as well. Encouraging results were observed recently in patients with FLT3-ITD–mutated AML, who were treated with tyrosine kinase inhibitors,3 and in preclinical models of NPM1- or IDH1-mutated AML treated with retinoic acid.4,5 However, mechanisms of cell differentiation impairment in AML remain largely unknown, and no therapy is yet available to induce differentiation across multiple AML subtypes.

S100A8 and S100A9 belong to the S100 family of low-molecular-weight secreted proteins, which contribute to cellular processes including calcium homeostasis, cell growth, and differentiation by engaging membrane receptors such as RAGE or TLR4 and activating downstream signaling pathways.6 In normal hematopoiesis, myeloid progenitor cells downregulate S100A9 to undergo macrophage and dendritic cell differentiation.7 Additional evidence in solid tumor biology suggests that S100 proteins cause myeloid differentiation arrest and accumulation of myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment, and that they directly exert pro-oncogenic effects on cancer cells as well.8 It is therefore striking that the study by Laouedj and colleagues is the first to focus on the role of S100A8/A9 in the biology of AML.

Laouedj et al demonstrate that S100A8/A9 proteins are abundantly produced by AML cells in murine models and in primary patient samples. They unambiguously show that S100A8/A9 proteins are secreted primarily by leukemic cells, not by the microenvironment. Using selective therapeutic S100A8/A9 antibodies and recombinant peptides, they elegantly show that these proteins play critical roles in leukemia progression in an H9M1-overexpressing mouse model of AML. Both S100A8 blockade by an anti-S100A8 antibody and treatment with recombinant S100A9 proteins reduce the leukemic burden and significantly prolong survival in this model, with cytologic and flow-cytometric evidence that these agents induce features of myeloid differentiation. Mechanistically, the authors use a multiplex phospho-flow approach that incorporates specific anti–TLR4 antibodies to show that S100A9 induces TLR4-dependent intracellular signaling pathways such as those involving MAPK or NFκB. Finally, the authors demonstrate that recombinant S100A9 proteins induce differentiation of primary leukemia blasts of the FAB M4/5, but not the M0/1 subtypes, ex vivo.

These data thus suggest a novel strategy for pharmacologic induction of AML cell differentiation with important therapeutic implications. Considering the precedent set by APL, we hypothesize that differentiating agents may be capable of synergizing with chemotherapy to achieve deep molecular responses and, in some cases, the cure of other AML subtypes (see figure). In fact, unbiased proteomic analysis has revealed that S100A8 expression is associated with poor survival in AML;5 this finding is consistent with the in vivo antileukemic activity of therapeutic anti-S100A8 antibodies that was observed by Laouedj and colleagues.

Although the present study marks an important advance, multiple barriers to translation of these preclinical observations into clinical therapies remain. Chief among them is the need to determine which component of the S100A8/A9 dimer to target. S100A8 and S100A9 exert unique and sometimes opposing effects; even low doses of S100A8 can abrogate S100A9–induced differentiation. Moreover, the present study is based primarily on murine models. Relatively few primary AML samples were tested ex vivo, and among them, only the AML M4/5
There is evidence that $S_{100}A9$ expression induces $M4/M5$ differentiation, leading to impaired antitumor immunity, a finding of particular salience in view of recent breakthroughs in leukemia immunotherapy involving monoclonal antibodies, bispecific T-cell–engaging constructs, and chimeric antigen receptor T-cell therapies. We may therefore imagine that $S_{100}$-targeted therapies that exert both leukemia-intrinsic prodifferentiation effects as well as leukemia-extrinsic microenvironmental immune effects could potentially synergize with these novel immunotherapies, creating exciting possibilities for clinical investigation.

Mouse models that harbor genetic deletion of $S_{100}A8/A9$ exhibit essentially normal erythroid differentiation defect. Moreover, there is evidence that $S_{100}A9$ expression induces MDSC accumulation, leading to impaired antitumor immunity, a finding of particular salience in view of recent breakthroughs in leukemia immunotherapy involving monoclonal antibodies, bispecific T-cell–engaging constructs, and chimeric antigen receptor T-cell therapies. We may therefore imagine that $S_{100}$-targeted therapies that exert both leukemia-intrinsic prodifferentiation effects as well as leukemia-extrinsic microenvironmental immune effects could potentially synergize with these novel immunotherapies, creating exciting possibilities for clinical investigation.

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