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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Scoville et al, page 1792

AHR: leukemic countermeasure against NK cells

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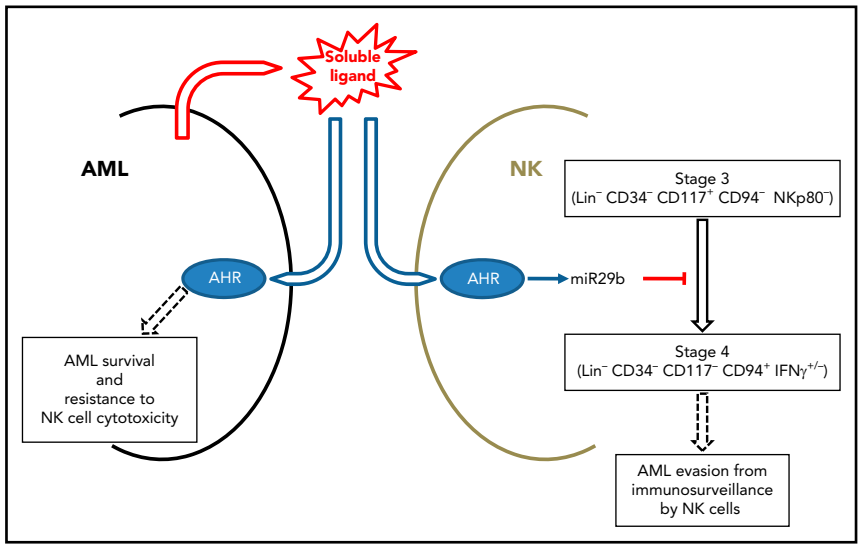
In this issue of *Blood*, Scoville et al report an original mechanism by which the aryl hydrocarbon receptor (AHR) allows acute myeloid leukemia (AML) to escape the natural killer (NK) cell–mediated antitumor immunosurveillance by increasing expression of microRNA (miR)–29b, thereby inhibiting NK-cell maturation and function.[1]

The seminal work by Ruggeri et al demonstrated that NK cells are critical effector cells in graft-versus-leukemia in AML after hematopoietic stem cell transplantation.[2] AML patients at diagnosis show deeply impaired NK-cell function against leukemia, with decreased capacity to release cytokines, such as interferon γ, and reduced cytotoxicity with low expression of intracellular cytolytic enzymes (perforin, granzymes). In that context, NK-cell defects are often associated with a specific AML transcription program,[3] emphasizing the intimate relationship taking place between both cell types during leukemogenesis. Mechanisms by which AML induces such profound and sustained NK cell defects are still largely unknown.[4]



AML can escape NK-cell antitumor responses by stimulating the AHR pathway both in NK and AML cells, which will inhibit NK cell maturation and function and promote AML cell survival.

Consequently, there is a quest to develop strategies to reactivate antitumor NK-cell function in support of patients' treatment at diagnosis or after complete remission.

Scoville et al identified AHR as a key factor in the NK cell/leukemia cross talk resulting in the inhibition of the NK-cell maturation and function, and in inducing resistance of AML blasts to NK-cell-mediated killing (see figure). Soluble ligands secreted by AML cells, which remain unidentified, trigger the AHR pathway in NK cells, which in turn increases the transcription of miR-29b and thereby inhibits NK-cell maturation, with a blockade at an immature and poorly functional differentiation stage. The importance of miR-29b in regulating NK-cell maturation and function in the context of AML, previously described in mouse models by the authors,[5] was herein confirmed in humans. AHR appears to be a direct regulator of miR-29b transcription through its binding onto the miR-29a/b1 promoter, suggesting the AHR pathway is a major mechanism by which AML dampens antitumor immunity. Treatment with an AHR antagonist of NK cells cocultured with AML could abrogate increased miR-29b expression and restore NK-cell maturation and function. Interestingly, AHR was also involved in AML survival and its resistance to NK-cell cytotoxicity.

There is growing interest in the role of AHR in the emergence and progression of cancer. Notably, AHR has been associated with the regulation of numerous biological processes important in tumorigenesis, including proliferation, migration, and inflammatory signaling.[6] In addition, AHR expression is increased in tumors relative to healthy surrounding tissues. However, AHR function varies according to the cell where it is expressed. Together with the wide diversity of endogenous and exogenous AHR ligands, it explains the difficulty in addressing the role of this transcription factor in cancer. Scoville et al showed that the AHR pathway could not only promote intrinsic capacities of resistance and survival of tumor cells, but also generate an inhibiting microenvironment preventing the antitumor immune response. Importantly, the AHR/miR-29b pathway did not directly inhibit NK-cell function when AHR was triggered in mature NK cells but impaired the upstream development of the NK-cell precursors. This observation is reminiscent of previous data by Roeven et al

showing that stimulation by an AHR antagonist could potentiate the generation of cytotoxic NK cells from CD34$^+$ hematopoietic stem and progenitor cells (HSPCs) in humans.[7] AML evasion from NK-cell immunosurveillance requires promoting immunosuppression at early stages of NK-cell development. Because AML originally emerges in the bone marrow, this observation points out a possible mechanism by which AML could sculpt the surrounding healthy hematopoietic cells, including HSPCs and consequently their progeny. This mechanism could allow AML cells to circumvent immunosurveillance not by direct inhibition of the mature immune cells, but by impeding their differentiation process. Importantly, AHR is also involved in the development of other immune lymphocyte subsets, including T helper 17 (Th17) CD4$^+$ T lymphocytes, interleukin-17-producing γδ T-cells, and type 3 innate lymphoid cells (ILCs).[8] AHR ligands are related to tryptophan metabolism, can be generated by cellular metabolism as well as commensal bacteria, and could play a major role in providing resistance to fungi or bacterial infections. However, these ligands present differential effects according to the target immune cell. For instance, the high-affinity AHR ligand 6-formylindolo [3,2-b]carbazole promotes Th17 and ILC3 development, whereas kynurenine, an AHR agonist produced by indoleamine-2,3-dioxygenase and tryptophan-2,3-dioxygenase, stimulates the generation of regulatory T cells.[8] Altogether, these observations suggest that immune subsets may respond differently to the triggering of the AHR pathway, depending of the ligand involved and their maturation stage and tissue microenvironment.

The work by Scoville et al constitutes a major step in the identification of drug targets to restore immunosurveillance against leukemia and eliminate residual leukemia posttreatment by restoring NK-cell function. However, prior to targeting the AHR pathway, further analyses will be necessary to identify which ligand is produced by AML cells to inhibit NK-cell maturation, how AML interferes with other immune cells through the AHR pathway, and how miR-29b is involved in these processes.

Conflict-of-interest disclosure: N.D. has been invited to scientific meetings organized by Bristol-Myers Squibb, Celgene, Celyad, and Innate Pharma. ■

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PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Hind et al, page 1818

Maestro endothelium conducts the neutrophils

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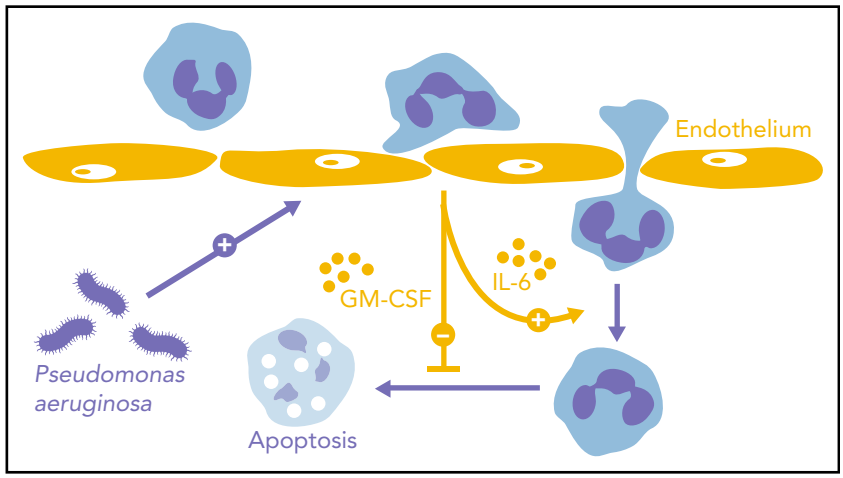
In this issue of *Blood*, Hind and colleagues leverage a custom microscale system to demonstrate that endothelial cells communicate with neutrophils via interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the presence of live *Pseudomonas aeruginosa* to enhance neutrophil transmigration.[1]

Neutrophils are a critical first line in the defense against infection but also contribute to pathologic inflammation. Their entry into tissues is therefore carefully regulated by a network of cells, cytokines, chemokines, and adhesion molecules.[2]



Orchestration of neutrophil transmigration by endothelium. Endothelial cells activated by extraluminal pathogens can provide IL-6 that promotes neutrophil migration deeper into tissues as well as GM-CSF that prolongs neutrophil survival.