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STAT3: the “Achilles” heel for AML?

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In this issue of Blood, in a series of elegant studies in a transplantable mouse model of acute myeloid leukemia (AML), Hossain et al1 show that systemic signal transducer and activator of transcription 3 (STAT3) blocking/TLR9 triggering can eradicate established AML through an immune-mediated mechanism.

Cancer growth is determined by cell-intrinsic phenomena, such as activation of transcription programs responsible for cancer cell proliferation, and cell-extrinsic phenomena, such as an immune-mediated cancer surveillance. The identification of a number of leukemia-specific antigens and recent clinical advances in cancer immunotherapy underscore the potential for safer and more effective AML treatments.2 However, many immunotherapies such as cancer vaccines have often shown insufficient antitumor effects,3 likely due to “immune editing” by the strongly immunosuppressive AML microenvironment.

One of the key transcription factors involved in tumorigenesis is STAT3, which is aberrantly activated (through tyrosine phosphorylation) in the majority of cancers.4 Constitutive STAT3 activity induces specific target genes that stimulate cell proliferation, prevent apoptosis, promote angiogenesis, and facilitate tumor immune evasion. STAT3 has also been shown to play a significant role in subversion of host immune responses and is responsible for the accumulation and the activation of immunosuppressive cells, such as regulatory T cells (Treg), Th17 cells, and myeloid-derived suppressor cells, and the absence of functional dendritic cells (DCs).4,5 Thus, targeting STAT3 both in cancer cells and immunosuppressive immune cells may result in restoration of immunocompetence, making it an attractive molecular target for the development of novel cancer therapeutics.

A number of therapeutic strategies have explored selective inhibition of STAT3 signaling, including small molecule inhibitors and compounds, protein inhibitors, dominant-negative STAT3


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