Targeting the “partners in crime”

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In this issue of Blood, Hertlein and colleagues present compelling in vitro and in vivo evidence that the novel HSP90 inhibitor 17-DMAG is a potent and selective killer of CLL cells that mediates its effects through the targeted inhibition of NF-κB. Their findings describe a promising new therapeutic approach for the treatment of this disease. Encouragingly, in vivo assessment of 17-DMAG in a TCL1-SCID transplant mouse model significantly reduced the tumor burden and prolonged survival of treated mice. However, SCID mice do not form lymph nodes so it remains to be seen whether 17-DMAG is capable of eradicating tumor cells from these microenvironments. With this in mind, clinical studies of HSP90 inhibitors suggest that they affect the stability of client proteins, but because of redundancy within signaling pathways, inhibiting HSP90 alone may not be sufficient. Moreover, it may be that HSP90 inhibitors will be most useful when coupled with conventional cytotoxic chemotherapy or other targeted therapies like monoclonal antibodies. In these combinations, HSP90 inhibitors may sensitize the tumor cells by suppressing antiapoptotic genes like MCL1 and BCL2. In so doing, they may increase the efficacy of existing chemotherapeutic agents and induce synergy.

Recent advances in treatment options for CLL have yielded higher response rates and improved progression-free and overall survival. However, CLL still remains an incurable malignancy in the majority of cases. This paper demonstrates that HSP90 inhibitors may be an important addition to the arsenal of expression of these proteins has been associated with inferior clinical outcome in CLL, so direct or indirect targeting of these proteins represents a promising therapeutic approach. Unlike 17-AAG, 17-DMAG inhibited the IKKα and IKKβ subunits of the IKK complex, making it theoretically capable of blocking both the classical and alternative NF-κB activation pathways (see figure). Evidence for this dual inhibitory effect was presented in which CLL cells were cultured in the presence of CpG oligonucleotides (classical activation pathway) and CD40 ligand (alternative activation pathway). Under both sets of conditions, 17-DMAG was able to inhibit nuclear NF-κB and suppress the expression of MCL1. These experiments may be important as a proof of principle, as there is growing evidence that CLL cells receive additional survival signals in the tissue microenvironment that may prevent complete clearance of tumor cells after treatment and thereby promote the persistence of minimal residual disease. In this context, it will be interesting to extend these studies to include an assessment of the apoptotic responses induced by 17-DMAG under these same conditions.
targeted therapies used in the management of this disease. Additional studies of HSP90 inhibitors, including detailed profiling of the specific client proteins that they target, are clearly warranted in CLL and other hematologic malignancies.

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REFERENCES


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LEC fate regulators: the 3 musketeers

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In this issue of Blood, Kang and colleagues describe a molecular signaling network involving Notch, COUP-TFII, and Prox-1, along with other supporting molecules that regulate the specification and maintenance of lymphatic endothelial cells.

The functional importance of the lymphatic vessels is tremendous. They drain excessive fluid and serve as a major route of transportation of absorbed lipids, macromolecules, cell debris, immune cells, and even cancer cells from the interstitial space into the regional draining lymph nodes and eventually to the systemic circulation. Thus, lymphatic vessels are crucial to maintain life. Growth of lymphatic vessels (lymphangiogenesis) is essential for normal embryonic development, normal postnatal physiologic function, as well as pathologic conditions such as inflammation or tumor dissemination. Lymphatic vessels are composed of a thin wall of monolayered lymphatic endothelial cells (LEC), which possess a very loose basement membrane and contain neither pericytes or smooth muscle cells. This unique architecture accounts for their specialized function and high efficiency in absorption and transportation. Lymphatic vessels gather to form the collecting lymphatic vessels, which have flap-like valves and are sparsely covered by a thin layer of smooth muscle cells that ensure a unidirectional delivery of lymph. In this regard, the collecting lymphatic vessels closely resemble venules both morphologically and functionally. In fact, the lymphatic vessels are derived from preformed veins around embryonic development days 9.5 to 10.5 in mice and weeks 6 to 7 in humans. A subset of endothelial cells (ECs) in the cardinal vein become committed to the LECs by a process orchestrated mainly by the master transcriptional factor Prox-1, secretory vascular endothelial growth factor (VEGF-C), and its cognate receptor, VEGF receptor-3 (VEGFR-3). This nascent lymphatic structure expands in a centrifugal pattern to establish the lymphatic network, which develops under the regulation of several key transcriptional factors, growth factors, and corresponding receptors. LECs establish a monolayered barrier at the innermost surface of blood and lymphatic ves.

In this issue of Blood, Kang et al propose a novel theory of the molecular mechanism underling the regulation by these 3 players in governing lymphatic specification and maintenance. Based on their extensive molecular and biochemical analyses using primary cultured human dermal LECs, the authors unraveled an exquisite feedback regulatory network controlling lymphatic specification and maintenance by the 3 endothelial fate regulators—Notch, COUP-TFII, and Prox-1. They show that activation of Notch signaling suppresses the expression of Prox-1 and COUP-TFII.
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