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A clinically relevant mouse model of human multiple myeloma?

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Since CCR1 neutralization did not completely inhibit EVT migration, platelet-derived soluble factors other than chemokines most likely also play a role in EVT migration. Though other studies have suggested that a lipid mediator, sphingosine-1-phosphate (S1P), is released from platelets,⁴ Sato and colleagues found that lipid removal from platelet-CM by charcoal stripping did not affect migration. However, heat inactivation of peptides halted migratory activity, indicating that protein factors, such as chemokines, are the premier factors in promotion of EVT migration.

These findings suggest that platelet activation and release of chemoattractants, triggered by contact with the ECM of invading EVTs, set off a positive feedback loop that promotes further EVT infiltration to maternal spiral arteries. Abundant expression on trophoblasts of thrombomodulin and tissue- and urokinase-type

tissue plasminogen activators may ensure that abnormal coagulation does not occur during this process. Greater understanding of the reciprocal regulation between platelets and EVTs may help develop more targeted therapies for preeclampsia, pregnancy loss, and fetal growth retardation. ■

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ventional models of mice carrying subcutaneous or disseminated human tumors are eliminated. Furthermore, measurement of serum-soluble IL-6 receptor and fluorescent imaging of host animals provide reliable assays to monitor MM cell growth and assess the therapeutic potential of investigational drugs and experimental therapies (see figure).

Tassone et al are not the first to describe an in vivo model of MM, since Yaccoby et al⁶ have already demonstrated engraftment of primary MM cells in SCID-hu mice. So what is new about Tassone et al's model? Although Yaccoby et al's model accurately recapitulates the pathophysiology of MM, its application on a large scale is hindered by the limited number of MM cells harvested from individual bone marrow patient samples and the potential variability among MM cells obtained from different patients. In Tassone et al's model, the use of an established IL-6-dependent cell line provides an unlimited number of MM cells

● ● ● NEOPLASIA

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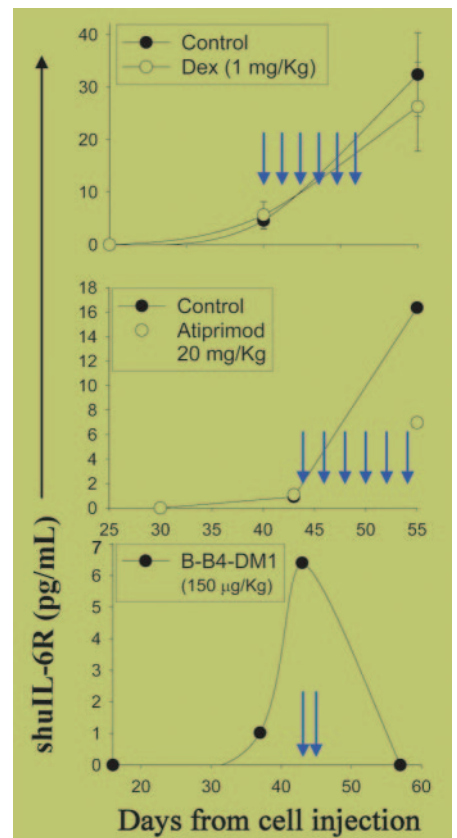
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In this issue of *Blood*, Tassone and colleagues describe a novel in vivo model of human multiple myeloma (MM) that relies on the engraftment of the IL-6-dependent human myeloma cell line INA-6 in a human bone marrow milieu implanted in SCID-hu mice. Because of the presence of the human microenvironment, evaluation of anticancer therapeutics in this model is likely to yield information predictive of their activity in MM patients.

The limited efficacy of conventional chemotherapy in most malignant diseases and the significant progress in our understanding of the molecular mechanisms underlying tumor growth and interactions with the microenvironment have recently fueled the development of several alternative therapeutic strategies. Therefore there is a need for preclinical models that are suitable to screen a large array of anticancer therapeutics in an efficient way and uncover information predictive of their clinical activity. MM is no exception to this trend. Antiangiogenic compounds,¹ proteasome inhibitors,² and immunotherapeutic strategies³⁻⁵ have already been shown to be viable approaches for the treatment of this disease. These results suggest that a large range of

therapeutic strategies will be developed in the coming years, emphasizing the need for a reliable animal model system that recapitulates the clinical features of MM.

The animal model described by Tassone and colleagues in this issue of *Blood* appears to meet most of these criteria. These authors have successfully engrafted the interleukin 6 (IL-6)-dependent human MM cell line INA-6 transduced with green fluorescent protein (*Gfp*) gene into severe combined immunodeficiency (SCID) mice that previously received transplants of human fetal bone chips (SCID-hu mice). The chips provide the human microenvironment, which plays a major role in the outcome of therapies of hematologic malignancies, so the major limitations of con-



Effect of dexamethasone, atiprimod, and B-B4-DM1 treatment on serum soluble human IL-2 receptor (shuIL-2R) of SCID-hu mice engrafted with INA-6 cells. See the complete figure in the article beginning on page 713.

with homogeneous and reproducible characteristics available for engraftment in SCID-hu mice; therefore, no difficulties are envisioned in evaluating anticancer therapeutics using the number of mice required to perform experiments with the appropriate statistical power.

Does the model described by Tassone et al have limitations, and if so, what are they? The model relies on one single-cell line that reflects one molecular subtype of MM with unknown and unpredictable frequency, so we do not know if and to what extent the conclusions drawn from this cell line can be generalized. Furthermore, evaluation of immunotherapies is restricted to the tumor antigen(s) and HLA allospecificities expressed by the INA-6 cell line. Finally, the potential for changes associated with in vitro culture raises the question of how closely the INA-6 cell line resembles the in vivo MM cells. These limitations emphasize the need to develop mouse models with

multiple MM cell lines that require the human bone milieu for their growth and survival. ■

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● ● ● IMMUNOBIOLOGY

Comment on Hebeis et al, page 635

Vav: a newcomer in innate receptor signaling

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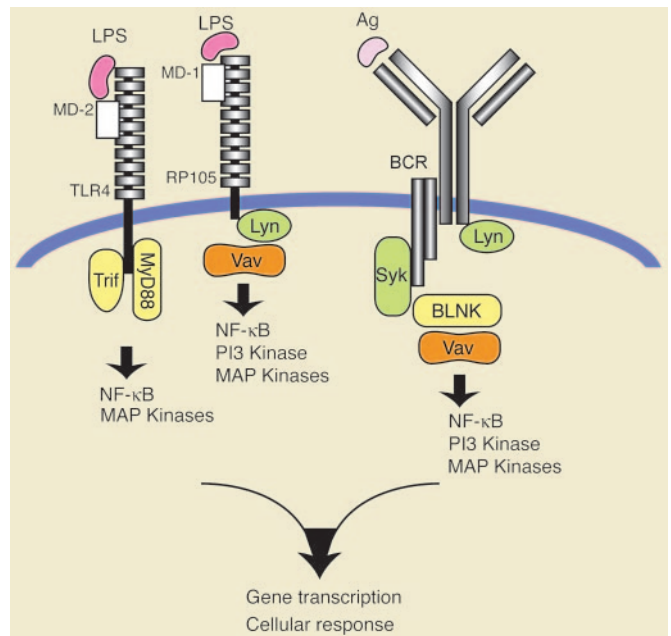
Emerging evidence indicates that the Vav family of signaling molecules plays a critical role in LPS receptor signaling, as well as in B-cell-receptor (BCR) signaling.

B lymphocytes must integrate 2 distinct signals before they proliferate and make antibodies; the first coming from antigens and the second coming from either helper T cells or microbial products such as lipopolysaccharide (LPS). The involvement of Vav1 and Vav2 in B-cell-receptor (BCR) signaling was first suggested by biochemical findings that these proteins were tyrosine phosphorylated in response to BCR ligation. Vav1 and Vav2 form protein complexes, by means of their Src homology 2 (SH2) domain, with the spleen tyrosine kinase (Syk), the coreceptor CD19, and the adaptor molecule B-cell linker protein (BLNK, also known as SH2-containing leukocyte protein of 65 kDa [SLP-65]) in activated B cells. These interactions are important in regulating cellular localization of Vav1/Vav2, undergoing tyrosine phosphorylation, and thereby enhancing their guanine nucleotide

exchange factor (GEF) activity. Although there was a brief period when it was suggested that Vav1 was a GEF for Ras, it is now accepted that Vav family proteins are not directly involved in Ras regulation, but rather target the Rho family guanosine triphosphatases (GTPases) Rac1 and Rac2.¹

The validity of the idea that Vav1 and Vav2 are indeed important players in BCR signaling was

reinforced by subsequent mouse genetic ablation experiments; loss of both Vav1 and Vav2 resulted in greatly compromised BCR signaling capability and were probably responsible for a block in humoral immune responses as well as B-cell maturation.^{2,3} The importance of Vav1 and Vav2 in antigen receptor signaling is clear, but 2 lines of recent observations suggested the additional possibility that Vav family proteins could participate in innate receptor signaling as well. First, not only BCR- but also LPS-dependent proliferation was profoundly inhibited in Vav1^{-/-}Vav2^{-/-} double knock-out B cells.² Second, introduction of dominant interfering mutants of Vav1 into transformed macrophages inhibited cytosine-phosphate-guanosine (CpG) DNA-mediated up-regulation of nuclear factor κ B (NF- κ B) activity and tumor necrosis factor α (TNF- α) secretion.⁴ In this issue of *Blood*, Turner and colleagues, by comparing LPS receptor signaling between wild-type and Vav1^{-/-}Vav2^{-/-} primary B cells, provide strong evidence that Vav1 and Vav2 are required for LPS-mediated Akt (one of the PI3K [phosphatidylinositol 3-kinase] targets) and NF- κ B activation, thereby contributing to B-cell survival and proliferation.



How Vav is activated in RP105 signaling is unclear, but the scenario that Lyn phosphorylates Vav, thereby enhancing its GEF activity, could be envisaged by the following: (1) activation of Lyn by RP105 stimulation; and (2) similar downstream defects in RP105 signaling between Lyn^{-/-} and Vav1^{-/-}Vav2^{-/-} B cells.⁵