MISTRG extends PDX modeling to favorable AMLs

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In this issue of Blood, Ellegast et al demonstrate that MISTRG mice allow high-level, reproducible engraftment of favorable prognosis acute myeloid leukemia (AML), a group that has been recalcitrant to attempts to develop valuable preclinical patient-derived xenograft (PDX) models.1

Over the last decade, impressive advances have been made in PDX modeling of AML. The engraftment rate for AML samples as a whole has been significantly increased through the use of mice that have been made more immune deficient by IL2RG knockout2-4 and by the transgenic expression of human myelo-supportive cytokines.5 Nevertheless, the engraftment of samples from favorable-risk patients, including CBF-rearranged, t(15;17), NPM1 mutant/FLT3 wild type, and CEBPa-mutated AMLs, has not improved significantly in these new mouse strains. This failure is all the more surprising when one considers that the 5-year survival of this group of patients is roughly 50%, indicating that many of these samples are highly aggressive in patients.6

With the advance described in this report, much needed preclinical in vivo testing of therapeutic strategies for this large subset of human leukemia will now be possible.

The success of this strain potentially lies in the mix of specific human cytokines and the fact that these cytokines are knocked in to the endogenous mouse loci, allowing proper regulation and contextual control over expression that is not possible in other mice. This knock-in approach offers much promise for PDX modeling, not only for hematologic and solid tumor malignancies but also in the realm of a reconstituted human immune system for modeling human immunity, studying human specific pathogen, and exploring aspects of human hematopoiesis that are currently impossible using conventional strains of immunodeficient mice.

As more designer strains of mice become available to the field and researchers are able to engraft the vast majority of AML samples, it will become possible to properly examine the predictive value of PDX models. Rigorous assessment of the subclonal architecture of individual PDX leukemias will likely reveal the differential engraftment of numerous clones found in the patient, with some clones being completely absent from the xenograft and others dominating. These different clones may show differential responses to therapies, and determining whether particular clones are responsible for treatment failure or relapse is a key question in evaluating potential therapies. For their part, the authors show that in 1 case of an NPM1 mutant AML, a striking similarity to the original patient sample is retained as measured by clonal NPM1 variants, gene expression profiles, and detection of additional mutations.

Proper host SIRPα binding to human CD47 initiates the “don’t eat me” signal that inhibits phagocytosis and has been thought to be key for avoiding rejection of human cells.7 Surprisingly, replacing the moderately effective mouse (BALB/c) SIRPα gene with the human allele had no significant effect on the engraftment of the tested AMLs. How the AML cells are able to overcome this immune defense is unclear. It remains to be seen whether this finding can be extended to AMLs generally and what this might signify with regard to additional anti-immune mechanisms that are operative on AML cells.

Even given the variability inherent to PDX models, generalities can still be realized from the study by Ellegast et al. For example, this study shows that human macrophage colony-stimulating factor (M-CSF) is a key signaling molecule for the propagation of inv16 patient samples in the mouse. It will be of interest to determine whether the observed overexpression of the M-CSF receptor and resultant increased downstream signaling represents addiction in inv16 AML. It is interesting to note that other AML subtypes have been associated with specific signaling cascades connected to particular cytokine receptors. Signaling through the THPO receptor appears to be associated with t(8,21) AML, and upregulation and/or activation of FLT3 is tightly correlated with t14q23 translocations involving the MLL gene.8,9 Whether these signaling cascades represent potential therapeutic targets in each of these AML subsets is an open question and is now able to be examined in a PDX model given the results presented in the study from the Manz group. It will be of interest to determine whether t(8,21) AML samples, another subgroup that has been difficult to model in xenograft approaches, show the same enhanced engraftment in MISTRG mice, given the presence of human THPO in this mouse strain.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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The lazy leukocyte syndrome revisited

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In this issue of Blood, Kuhns et al describe the probable molecular and genetic basis for a disease that has mystified investigators for over 45 years, the lazy leukocyte syndrome. This disorder is characterized by recurrent infections, stomatitis, a low neutrophil count, and impaired neutrophil motility, and these abnormalities can now help to address this important question. Family members and patients all had mutations present in high concentrations (~200 μM) in the cytoplasm of neutrophils, and this protein exists in 2 states: as monomers that can readily diffuse throughout the cytoplasm, and as actin filaments that can form branched networks that support the formation of lamellipodia, broad projections seen at the front of neutrophils as they migrate (see figure panel A). Great progress has been made in understanding how actin regulatory proteins and specific signal transduction pathways induce actin assembly. However, in order to change shape and produce amoeboid movement, actin filaments must also be quickly disassembled, and at the present time, our understanding of these mechanisms is more rudimentary. Actin depolymerizing protein (ADF; also called coflin) has been isolated and shown to bind to the sides of actin filaments and to destabilize monomer–monomer interactions within the filament, causing actin filaments to break apart or undergo severing. The ability of ADF/cofilin to sever actin filaments varies depending on the stoichiometry of binding. When actin filaments are saturated with ADF/cofilin, severing is minimal and filaments are stabilized; however, in living cells, despite the high concentrations of ADF/cofilin, actin filaments undergo rapid severing. Several proteins have been identified that may account for this activity, including coronins, Srv2/cycle-associated protein, and Aip1. In the absence of specific mutations and knockout experiments, the relative importance of each of these proteins in potentiating the severing of activity of ADF/cofilin is difficult to assess. The 3 families with genetic mutations described by Kuhns et al now help to address this important question. Family members and patients all had mutations
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