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Deconstructing Blood Cell Research
Building the Hematology Community

Exploring Experimental Hematology: July 2020 (Volume 87)

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In this issue of Simply Blood, we are highlighting and deconstructing one of the journal's latest manuscripts by first author Darlene A. Monlish. In a recent study in the laboratory of Dr. Laura Schuettpelz (Washington University School of Medicine), Monlish et al described heterodimer-specific effects of TLR2 signaling on premalignant hematopoietic stem and progenitor cells (HSPCs) in a mouse model of myelodysplastic syndromes (MDS). (Monlish et al., 2020).

TLR2 expression is increased on the HSPCs of patients with MDS, however its role in MDS pathogenesis is not clear. Notably, TLR2 heterodimerizes with TLR1 or TLR6, and while high TLR2 is associated with lower-risk disease, high TLR6, but not TLR1, correlates with higher-risk disease. This raises the possibility of heterodimer-specific effects of TLR2 signaling in MDS. Indeed, the authors found that chronic stimulation of TLR2/6 (but not TLR1/2) signaling accelerated leukemic transformation in a NUP98-HOXD13 (NHD13) mouse model of MDS. Conversely, loss of TLR6 (but not TLR1), delayed transformation. Furthermore, TLR2/6 agonist (but not TLR1/2 agonist) treatment led to increased cycling and expansion of premalignant HSPCs, and TLR2/6 stimulation was associated with activation of Myc and mTORC1. Myc inhibition partially mitigated the TLR2/6 agonist-mediated expansion of premalignant HSPCs, while mTORC1 inhibition dramatically increased this effect, suggesting that Myc and mTORC1 have opposite roles in mediating the effects of TLR2/6 stimulation on premalignant HSPCs.

My reason for reading the paper:
Inflammatory signaling is being increasingly implicated as a factor that influences both the short-term and long-term function of HSCs in the bone marrow, as well as a factor that contributes to neoplastic transformation of clonal hematopoiesis. This study helps to delineate how specific, yet closely-related, inflammatory signaling pathways contribute to MDS progression.

Strategy used in this paper:
The authors used a transgenic NHD13 mouse model as their MDS model and then treated transgenic or control micewith different agonists which stimulate different components of TLR signaling. Progression of MDS and evolution to leukemia was monitored, with complementary pathological analyses and functional

analysis of malignant stem cell function. Gene expression profiling was used to identify Myc and mTOR signaling as critical pathways important for the TLR2/6 response in HSCs.

Reasons you should read this paper:

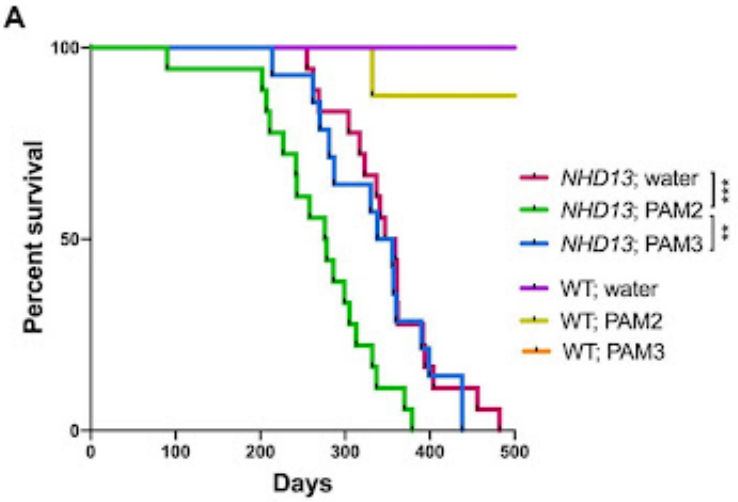
This paper dissects important molecular changes distinguishing MDS HSPCs from normal HSPCs that regulate response to specific inflammatory signals. This paper highlights TLR2/6 heterodimers as potential points of intervention which could be investigated for new therapies for MDS. As TLR antagonists are currently in clinical trials for MDS, this pre-clinical study provides further means to potentially determine which patient populations may benefit from such treatments.

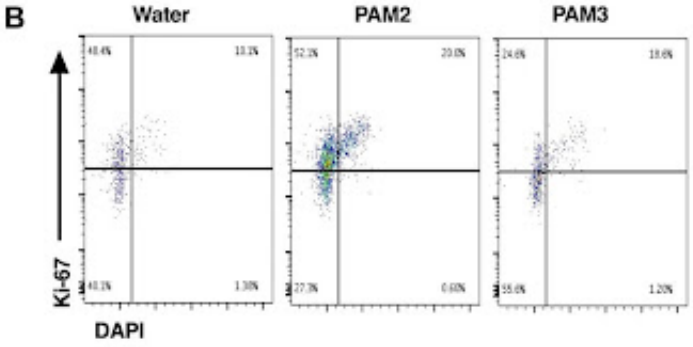
Quote from the author:

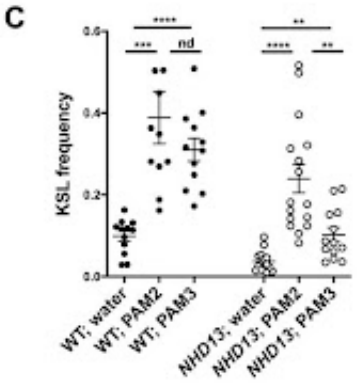
While inflammatory signaling, and in particular toll like receptor signaling, is an attractive target in MDS, its role is not entirely clear. Our research hopes to further clarify which TLRs should be targeted to improve hematopoiesis in patients with MDS.

Attached Figure:

A. Kaplan-Meier survival curves of wild-type and NHD13 mice treated chronically with the TLR1/2 agonist PAM3CSK4 (PAM3), the TLR2/6 agonist PAM2CSK4 (PAM2), or water. B. Cell cyling, as determined by Ki-67 and DAPI staining, was increased in HSPCs (Lineage- c-Kit+ Sca-1+ cells) from NHD13 mice upon treatment with PAM2 compared to other treatments. C. The TLR2/6 agonist (PAM2) more robustly increased the frequency of HSPCs in the bone marrow of NHD13 mice compared to the TLR1/2 agonist (PAM3). (excerpts from Figs 1 and 2).







Grant A. Challen, Ph.D.
Associate Professor
Section of Stem Cell Biology
Division of Oncology
Department of Internal Medicine
Washington University in St. Louis

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Lab Spotlight: Vanuytsel Lab

- *November 14, 2024*

Each month, Simply Blood spotlights a lab contributing to the fields of hematology, immunology, stem cell research, cell and gene therapies, and more. Get to know groups doing cutting edge research from around the world! This month, we are featuring the Vanuytsel Lab which is based out of the Center for …

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