Below the NK-cell surface: PIP2

Marco Colonna  Washington University School of Medicine at St Louis

In this issue Blood, Micucci and colleagues demonstrate that PIP2 plays an essential role in NK-cell cytotoxicity by controlling the release of lytic mediators at the NK cell–target interface.

Membrane phospholipids are essential for a variety of cellular functions. They act as second messengers that couple engagement of cell-surface receptors with recruitment and activation of downstream intracellular molecules, and are also involved in cell adhesion, motility, actin cytoskeleton dynamics, phagocytosis, vesicle trafficking, endocytosis, and exocytosis.1-4 Despite their established physiological relevance, membrane phospholipids have generally been a rather obscure topic in the context of natural killer (NK)–cell function. Now, Micucci and colleagues bring phosphatidylinositol 4,5-bisphosphate (PIP2) to the forefront of NK-cell biology in this issue of Blood.

PIP2 is the precursor of 2 second messengers that are indispensable for cellular signaling—inositol 1,4,5-trisphosphate (IP3), which mobilizes Ca2+ from intracellular stores, and diacylglycerol (DAG), which activates protein kinase C (PKC). Cleavage of PIP2 into IP3 and DAG is mediated by members of the phospholipase C (PLC) family.5 PIP2 also interacts with the actin-binding proteins gelsolin and profilin, as well as with many other signaling molecules that are indispensable for cellular signaling—actin cytoskeleton dynamics, phagocytosis, vesicle trafficking, endocytosis, and exocytosis.6-9

Micucci and colleagues found that while inhibition of PI4P-5KI repressed the activity of PI3K, it had no effect on the activity of PI3K. This is surprising, given that PI3K uses PIP2 as a substrate to generate PI3, another key regulator of cytotoxicity and NK-cell function.10 The data reported by Micucci et al thereby suggest that PIP2 is generated in distinct cell compartments and that each PIP2 pool is likely to have a specific or restricted function within the cell. Thus, just beneath the NK-cell surface, we begin to see the murky world of membrane phospholipids coalesce into functionally meaningful patterns.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

AML1 and Evi1: coconspirators in MDS/AML?

Timothy Graubert  Washington University School of Medicine

In this issue of Blood, Watanabe-Okochi and colleagues use a mouse bone marrow transplantation model to demonstrate that mutant alleles of AML1 (RUNX1) can initiate a myelodysplastic syndrome (MDS) that progresses to acute myelogenous leukemia (AML) in association with overexpression of Evi1.
Half the AML1 cases, the authors mapped retroviral integration sites to the 5’ flanking region of Evil and were able to demonstrate that this was associated with Evil overexpression. They went on to show that coinfecion of cells with AML1D171N and Evil retroviruses shortened disease latency by 50 days and increased penetrance to 100%, providing additional evidence that Evil and mutant AML1 can cooperate to induce MDS/AML in mice. Although the mechanism of Evil activation is artificial in this model (retrovirus-mediated insertional mutagenesis), the observations by Watanabe-Okochi and colleagues have important clinical relevance. Evil is deregulated by the t(3;3)(q21; q26) and inv(3)(q21;q26) rearrangements in MDS and AML. Several lines of evidence have also directly linked AML1 and Evil in human leukemia biology. First, the genes are fused by the t(3;21)(q26;q22) rearrangement in blast-crisis CML. In addition, the proteins physically interact, leading to reduced AML1 DNA binding and transcriptional activity. This leads to the prediction, not tested in the current study, that Evil and the AML1D171N allele cooperate in vivo because they conspire to reduce AML1 activity. If further studies support this model, there would be a rational basis for developing therapies that target this protein–protein interaction.

REFERENCES

TRANSPLANTATION

Comment on Domini et al, page 4386

Osteopiotic stem cells: transplantable, but regeneratively limited

Susie Nilsson australian stem cell centre

Questions about the transplantability of mesenchymal stem cells, their ability to engraft within the bone marrow of recipients, and hence their clinical usefulness have been hotly debated for several decades. In this issue of Blood, Domini and colleagues demonstrate robust serial osteopiotic engraftment, but highlight that osteopiotic chimerism declines to negligible levels after 6 months.

Due to the presence of hematopoietic stem cells in the bone marrow, bone marrow transplantation has been successfully used to treat hematological diseases for many decades. Based on the concept that bone marrow also contains microenvironmental or mesenchymal stem cells (MSCs) with osteopiotic potential, the clinical use of bone marrow transplantation to treat bone disorders is also very appealing. Although initial studies suggested that MSCs cannot be transplanted intravenously, more recently documented animal models and preclinical studies have demonstrated that donor MSCs engraft in the bone marrow and give rise to bone and muscle. Furthermore, a series of clinical trials performed by this group, involving children with severe osteogenesis imperfecta, demonstrated that transplanting unmanipulated bone marrow resulted in a marked improvement in total body mineral content, accelerated linear growth, and decreased fracture rates. Similar results were evident following transplantation of purified MSCs. In all of these studies, however, the observed accelerated growth diminished over
AML1 and Evi1: coconspirators in MDS/AML?

Timothy Graubert