Comment on Ting et al, page 2510

Do HSCs divide asymmetrically?

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In this issue of Blood, Ting et al identify the cell polarity–associated gene \textit{Ap2a2} as a positive regulator of hematopoietic stem cell (HSC) function and a candidate determinant of asymmetric HSC divisions.\(^1\)

\textbf{Hematopoiesis is maintained by stem cells with the ability to both self-renew and to give rise to differentiated progeny. A proper balance between these fates is essential to prevent hematopoietic failure or uncontrolled stem cell expansion. So how do HSCs undergo self-renewal? In theory, this can occur in 2 ways; either through symmetrical cell division (SCD) where 2 new stem cells are formed, or through asymmetrical cell division (ACD) giving rise to 1 stem cell and 1 cell committed for differentiation. Symmetrical division must occur because this is the only way by which the stem cell pool can be expanded.

However, whether asymmetrical division really occurs in HSCs has remained an unresolved and elusive question.

Evidence supporting ACD in HSCs has been provided by detailed functional studies of the progeny of highly purified HSC populations, so-called paired daughter cell analysis.\(^3,4\) While these studies have clearly demonstrated that the 2 progeny of an HSC division can have different functional properties, it cannot be ruled out that these differences have been inferred by extrinsic factors immediately after cell division and they may therefore not be the result of an ACD per se. On the other hand, in lower organisms like \textit{Drosophila melanogaster} and \textit{Caenorhabditis elegans}, elegant studies have formally proven the existence of asymmetric stem cell divisions.\(^2\) Cells have been shown to be polarized during division and to unequally localize cell fate–determining molecules, which are asymmetrically inherited in the daughter cells. To ultimately prove that ACD occurs in HSCs it will be key to define molecules that segregate asymmetrically during mitosis and to show that the unequal partitioning of these molecules has functional consequences.\(^5\)

It is in this context that Ting et al now report on \textit{Ap2a2} as a novel regulator of HSC function.\(^1\) Informed mainly by studies in lower organisms,\(^6\) Ting and colleagues decided to screen genes involved in cell polarity, for their ability to regulate HSC function in mice with the aim of identifying potential determinants of ACD in HSCs. They tested 43 candidate genes using retroviral overexpression in a combined in vitro/in vivo screening assay,\(^7\) and found 6 genes that had a clear, positive impact on HSC function. They decided to first focus on the endocytic gene, \textit{Ap2a2}, as it was the top scorer with the most potent effect in the screening assays.\(^1\)

Asymmetrical segregation of AP2A2 during mitosis. CD150\(^{48-}\)LSK cells were transduced with an Ap2a2-Cherry fusion gene. Still frame from live cell videomicroscopy of dividing cells: DNA (Fitc-green); AP2A2 (Cherry-orange). Image from Ting et al.\(^1\)
of the fluorescently labeled AP2A2 protein (see figure).

The findings that Ap2a2 positively regulates HSC activity and also shows unequal segregation during mitosis are highly intriguing and indicate that Ap2a2 may in fact act as a cell-fate determinant influencing ACD. However, more work is required to support this. For example, it would be of great interest to isolate the immediate progeny of HSC divisions based on unequal segregation of AP2A2 and then determine the functional consequences of presence or absence of AP2A2 in the daughter cells. This would not only give more insights about Ap2a2 as a potential cell-fate determinant but could ultimately help resolve the long-standing question of whether or not asymmetric self-renewal occurs in HSCs.

One important aspect of ACD is malignant development. Studies in Drosophila have shown that normal stem cells can transition to tumor stem cells when genes involved in asymmetric cell division become mutated.8 Proving the concept of ACD in HSCs and gaining a better understanding of the process will therefore have implications for cancer-related questions. Cell-fate determinants active in HSCs may also be involved in leukemogenesis. The impressive strategy used by Ting and colleagues, combining functional genetic screens in HSCs with the tracking of protein segregation, promises to reveal additional candidate ACD-associated genes in the future.

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REFERENCES

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Human FcγRIIA at center stage

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In this issue of Blood, Jönsson et al show in an elegant transgenic study that human FcγRIIA, an activating IgG receptor, can trigger active and passive anaphylaxis and airway inflammation.1

The term “aphylaxis” was originally coined by Charles Richet in 1902 and later changed to “anaphylaxis.” Anaphylaxis is a hyperacute systemic allergic reaction that can occur within minutes or hours of antigen exposure in sensitized humans, leading to various symptoms including an itchy rash, throat swelling, low blood pressure, and death. Common causes include insect bites, foods, and medications. Anaphylaxis leads to 500–1000 deaths per year in the United States.

Because of the dramatic nature and serious outcomes of anaphylaxis, physicians and scientists have long been intrigued by this disease. However, only the past 3 decades after antibody Fc receptors were identified have the mechanism involved begun to be elucidated. Experimentally, 2 types of anaphylaxis have been studied: one can be induced by immunizing animals by antigen and followed by antigen challenge (active anaphylaxis) and the other by injecting antigen in animals previously sensitized with antigen-specific antibodies (passive anaphylaxis). Experimental anaphylaxis can be induced at the systemic level (systemic anaphylaxis) or locally, depending on the route of antigen challenge. IgE, the classic atopy-related antibody, plus allergen can cause passive systemic and cutaneous anaphylaxis (PSA and PCA). IgE was thought to be responsible for anaphylaxis, but surprisingly, active systemic anaphylaxis (ASA) can be induced in mice genetically made incapable of producing IgE. Later, IgG was also shown to have the ability to induce anaphylaxis. Use of knockout and transgenic mice allowed researchers to determine what types of antibodies, cells, Fc receptors, and effector molecules are involved in or responsible for different models of anaphylaxis (see figure). For example, IgE-induced PCA2,3 and PSA4,5 require FcεRI (the high-affinity IgE receptor) expressed in mast cells and histamine released from activated mast cells. IgG1-induced PCA also depends on mast cells,2 but FcγRIIA (not FcεRI) is the receptor used.6 IgG1-induced PSA was reported to require FcγRIIA on basophils,7 although this study was not replicated in basophil-deficient mice. Jönsson et al recently reported that IgG2b-induced PSA requires neutrophils expressing FcγRIV and platelet activating factor (PAF) and polyclonal IgG-induced PSA also requires neutrophils.8 Unlike a study showing that monocytes/macrophages are responsible for ASA induced by goat IgG in mice immunized with goat IgE anti-mouse IgD,9 Jönsson et al showed that neutrophils expressing FcγRIV and, to a lesser extent, basophils expressing FcγRIIA contribute to ASA.

It is not easy to translate mouse results to human diseases, particularly anaphylaxis. The problems are many: there are multiple Fcγ receptors in both mice (FcγRI, FcγRIIB, FcγRIIA, FcγRIV) and humans (FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA, FcγRIIIB). Mouse FcγRI, FcγRIIA, and FcγRIV and human FcγRI and FcγRIIA are activating IgG receptors associated with a disulphide-bonded dimer of an ITAM-containing FcγRI subunit, while mouse and human FcγRIIB are inhibitory receptors with ITIM. FcγRIIA possesses an ITAM in its intracytoplasmic domain and is not associated with the FcγRI subunit. Human Fcγ receptors are not directly related to mouse Fcγ receptors. For example, mouse FcγRIV has no human ortholog. Mouse neutrophils express FcγRIIA and FcγRIV, whereas human neutrophils express neither FcγRIIA nor FcγRIV, but FcγRIIA and FcγRIIIB, which do not exist in mice. Of course, experiments...
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