Comment on Sparber et al, page 217

**p14 in control of Langerhans cell homeostasis**

Keisuke Nagao1 1KEIO UNIVERSITY SCHOOL OF MEDICINE

In this issue of Blood, Sparber et al have identified that p14 is crucial for maintaining the homeostasis of epidermal Langerhans cells (LCs).1

P14, also known as LAMTOR2, is an endosomal adaptor protein that confines mitogen-activated protein kinase (MAPK) signaling to late endosomes that play critical roles in leukocytes such as neutrophils, B cells, cytotoxic T cells, as well as melanocytes. A novel disease was discovered in 2007, in a Mennonite family that exhibited immunodeficiency and hypopigmentation, and the causative gene was identified to be p14.2 Thus, p14 is of strong interest not only in the context of cell biology, but also in a disease context.

The roles of p14 have never been explored in dendritic cells (DCs). Sparber et al address p14 function in DCs with special focus on LCs, the unique DC subset in the epidermis. When p14 was conditionally ablated in cells that express CD11c, thus targeting all DCs, the numbers of migratory DCs in skin-draining lymph nodes showed a 50% reduction and epidermal LCs were virtually absent. By selectively depleting p14 in LCs by using Langerin-Cre mice, it was determined that the loss of LCs was cell-intrinsic. During development in neonatal mice, LCs have been reported to proliferate and expand in situ to establish their network in the epidermis.3 Although p14-deficient (p14del) LCs migrated into epidermis, they were less capable of proliferating than wild-type (WT) LCs. This was due to cell-cycle arrest, as determined by 5-bromo-2'-deoxyuridine uptake studies, where p14del LCs accumulated in S phase and did not enter mitosis. p14del LCs were also prone to apoptosis, thereby failing to persist in the epidermis as mature LCs. Therefore, p14 critically regulates the cell cycle of LCs during postnatal expansion. p14 also appears to function in langerin+ dermal DCs as this subset also showed a striking decrease in number in adult Langerin-p14del mice, although the impact seems more striking on LCs in neonatal mice (see figure).

Recent studies show that cells of monocytic origin are capable of giving rise to a subset of LCs. Gr-1high monocytes enter the epidermis as major histocompatibility complex (MHCI) II+ langerin+ cells, and differentiate into bona fide LCs with langerin and epithelial cell adhesion molecule expressions.4,5 MHCI II+ langerin+ cells in epidermis have been termed “pre-LCs” to reflect their nature as immediate LC precursors.5 Pre-LCs could be induced in the presence of inflammation induced by mechanical stress or hapten-induced inflammation to become LCs, but among the whole LC population, monocyte-derived LCs represent a minor population.5 The major LC population is the slow-repopulating steady-state LCs that originate mostly from fetal liver monocytes.6 It has also been reported that LCs repopulate the epidermis in 2 distinct waves, where repopulation of cells with a phenotype similar to pre-LCs (defined as short-termed LCs) initially occurred, followed by persistent population of long-term LCs.7 Taking all of the reports into account, LCs comprise 3 lineages: those of monocytic origin that enter the epidermis upon inflammation, fetal liver monocytes, and yolk sac macrophages. LCs arising from monocytes likely correspond to short-term LCs, and those arising from fetal liver monocytes and yolk sac macrophages likely correspond to long-term LCs.

With the above concept of LC origin taken into account, Sparber et al show that short-term LCs were capable of entering the...
epidermis in CD11c-p14del mice in response to inflammation elicited by topical 2,4,6-trinitro-1-chlorobenzene, but did not acquire LC markers. It appears that LC precursors of monocytic origin can enter the epidermis, but cannot persist to properly differentiate into bona fide LCs in the absence of p14, stopping differentiation at the pre-LC state. Because LC precursors do not proliferate and undergo apoptosis in the absence of p14, long-term LCs also cannot reside in the epidermis to form a proper network. Therefore, p14 deficiency affects all LC lineages.

The hair follicles have been demonstrated to be responsible for recruiting pre-LCs via chemokine production and to act as gateways to allow pre-LCs to enter the epidermis. The authors very nicely capture this process by immunofluorescence microscopy, where short-term LCs were found to accumulate to hair follicles as they entered the epidermis.

Finally, via biochemical analyses using bone marrow–derived DCs, the authors show that mammalian target of rapamycin complex 1 and MAPK kinase 1/extracellular signaling-regulated kinase 1 signaling are impaired in the absence of p14, establishing the importance of these signaling pathways in subsets of DCs. It is interesting to think about the significance of these mechanisms in disease contexts. In vivo functions of LCs reported thus far appear to be context dependent, and the broad picture is yet to be established. However, one could easily think of 2 clinically relevant situations: LC histiocytosis and graft-versus-host disease (GVHD). In the former, although the tumor cells are not identical to normal LCs, they do exhibit DC phenotypes, and it might be worth studying whether p14 is required for proliferation of neoplastic cells in LC histiocytosis or non-LC histiocytosis. In bone marrow transplantation settings, LCs have been implicated in activating donor-derived lymphocytes to initiate acute GVHD. The current treatment of GVHD is to put patients on strong immunosuppressive agents. If, in fact, LCs have roles in initiating GVHD in humans, it is attractive to hypothesize that prior elimination of LCs by targeting signaling pathways described by Sparber et al might ameliorate GVHD or reduce its incidence in patients who have undergone bone marrow transplantation. Targeting p14 or its downstream signaling pathways might provide alternative pathways as therapeutic targets in these 2 important diseases.

DCs are central regulators of immunity. Vaccination targeting DCs is a growing and important field. However, DCs have not received as much attention as therapeutic targets in repressing inflammatory diseases. The work by Sparber et al not only represents an important finding in DC biology, but also provides impetus to designing new strategies on DC targeting, and into which diseases this concept should be applied.

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

REFERENCES

© 2014 by The American Society of Hematology

Comment on Sapey et al, page 239

A straight neutrophil path to healthy aging?

Paul H. Naccache1 and Julie S. Lefebvre2 1 LAVAL UNIVERSITY; 2 TRUDEAU INSTITUTE

In this issue of Blood, Sapey et al1 report that the human polymorphonuclear neutrophil leukocyte (or neutrophil) undergoes an age-related loss of its ability to migrate up chemotactic gradients, a functional defect that seems causally related to alterations in the polyphosphoinositide pathway.2

The decline in the efficiency of the immune system is a well-established consequence of aging, a phenomenon termed immunosenescence. The impact of aging on immunity has been principally addressed within the context of the acquired arm of the immune system, and little is known about the senescence of neutrophils. This is surprising considering that the neutrophil occupies a central role in the initiation and regulation of the inflammatory response and in the first line of defense of the organism against injurious stimuli. The neutrophil also regulates the effector arm of the immune system by virtue of its ability to synthesize and secrete a wide variety of cytokines and chemokines. In addition, its phenotypic plasticity allows it to express functional MHC class II molecules and possibly functional T-cell receptors. These functions of the neutrophil are not fully understood or appreciated.3 It is nevertheless clear that profound functional links exist between the neutrophil and the other actors of the immune response. Characterizing how aging impacts neutrophil functions is therefore critical if we hope to improve the immune response of the aged.

Neutrophils need to move to the site of tissue infection or injury to accomplish their...
p14 in control of Langerhans cell homeostasis

Keisuke Nagao