associated with reduced infiltration by neutrophils and macrophages and reduced levels of proinflammatory cytokines, such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor α after CIA. Consistent with the role of fXIII in stabilizing fibrin matrices, fXIIIAD−/− mice had diffused and limited fibrin deposition in the joint after CIA. These findings provide compelling evidence that the proinflammatory effects of fXIII in rheumatoid arthritis are fibrin-dependent and suggest that fibrin cross-linking in vivo is required for the activation of the inflammatory response (see figure).

In a second set of experiments, the group made an unanticipated discovery for a fibrin-independent function of fXIII in the joint, leading to direct damage to the cartilage and bone. Surprisingly, knee joints of CIA-challenged fXIIIAD−/− mice had dramatically reduced numbers of osteoclasts, which are responsible for cartilage and bone resorption (see figure). Intriguingly, osteoclast reduction associated with reduced levels of osteoclast regulators, such as receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin, was uniquely associated with fXIII deficiency because genetic loss of fibrinogen did not impact the osteoclast numbers after CIA. Osteoclast maturation of CD11b+ progenitor cells derived from fXIIIAD−/− mice showed defects in osteoclast differentiation in vitro. Fibrin-induced stimulation of CD11b+ cells induces robust activation of inflammatory and oxidative stress pathways.7,8 Although the effects of fibrin on osteoclastogenesis in vitro were not tested in the study, the findings strongly support a fibrin-independent role of fXIII in bone destruction in the inflamed joint (see figure).

This exciting study raises several important questions. Does fXIII play a role in other autoimmune models of inflammation and tissue destruction? Although it is likely that fXIII regulates inflammation via stabilizing fibrin or other substrates in other disease settings, it is unknown whether its effects in tissue destruction are uniquely linked to osteoclast differentiation in the joint. Although this study supports prior findings demonstrating a critical role for coagulation in the activation of innate immunity, the role of fibrin and the coagulation cascade in the regulation of adaptive immunity remains largely unknown. Depletion of fXIII in CIA does not reduce the numbers of T and B cells in peripheral immune organs.1 However, it remains unknown whether fXIII-mediated, fibrin-induced activation of resident innate immune cells regulates local T-cell activation in tissues. Finally, this study, together with compelling evidence for the contribution of coagulation in rheumatoid arthritis patients,9 not only opens new avenues for repurposing anticoagulant therapy to limit both inflammation and bone erosion but also fuels enthusiasm for the development of new drugs to selectively target components of the coagulation cascade in autoimmune diseases.

The study by Raghu et al1 adds fXIII as a key player in rheumatoid arthritis with a dual role in inflammation and bone destruction. This exciting new finding has the potential to launch a new line of research to determine the pleiotropic effects of fXIII in inflammatory induced tissue damage and develop novel therapeutic strategies for autoimmune and inflammatory diseases.

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REFERENCES

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IMMUNOBIOLOGY

Comment on Milne et al, page 470

Langerhans cells: straight from blood to skin?

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In this issue of Blood, Milne et al1 report a developmental pathway for human Langerhans cells from circulating CD14+CD1c+ dendritic cell (DC) precursors in peripheral blood. The Langerhans cells progeny, expressing CD207 (langerin) and bearing the hallmark Birbeck granules, result from culture in granulocyte macrophage colony-stimulating factor (GM-CSF) and transforming growth factor-β1 (TGF-β1) and/or bone morphogenetic protein 7 (BMP7). A similar study by Martinez-Cingolani et al,2 also published recently in Blood, identified the same circulating CD14+CD1c+ Langerhans cell precursors. These authors used a different anti-CD1c monoclonal antibody (BDCA-1). In that study, TGF-β1 synergized with thymic stromal lymphopoietin (TSLP) to yield similar Langerhans cell progeny. Both groups used fetal calf serum (FCS), which affects differentiation and maturation by unknown mechanisms and is not physiologically comparable to human plasma in vivo. Controls with FCS-containing medium, but without cytokines, indicated that FCS was not the driver of the conversion. However, Milne et al1 could not generate Langerhans cell progeny by culture in X-Vivo medium without FCS, despite inclusion of GM-CSF, TGF-β1, and BMP7, all of which, together with TSLP, are epithelial cell–derived cytokines under physiologic conditions.

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Residence in stratified epithelia, CD207 expression, and Birbeck granules all define bona fide Langerhans cells in humans (see figure). Indeed, the progeny of CD1c⁺ blood DCs express substantial CD207 after culture with either GM-CSF/TGF-β1/BMP7 or TGF-β1/TSLP. Birbeck granule morphology by electron microscopy is also convincing. Neither group evaluated the capacity to populate the epidermis, for which several methods exist using artificial skin equivalents, even though their Langerhans cell progeny express a number of skin-homing receptors like CCR6. Langerhans cell progeny report skin-homing receptors with far less expression of CD1a, CD207, or Kupffer cells. Human Langerhans cells were observed in human fetal epidermis as early as 9 weeks' estimated gestational age. This is before the beginning of hematopoiesis in the bone marrow at 10.5 weeks' estimated gestational age, suggesting that human Langerhans cells also derive from fetal hematopoietic tissues. Langerhans cells are composed of low-level proliferation from local precursors.

In inflamed mouse skin, however, Langerhans cell replenishment of those that have migrated from the epidermis to draining lymph nodes occurs in 2 phases. Blood monocyte precursors provide only the first wave, whereas hematopoietic precursors comprise the second, more durable repletion of the long-lived local precursors and their Langerhans cell progeny. It remains elusive, however, under which circumstances CD1c⁺ DCs would differentiate in vivo into epidermal Langerhans cells in humans. It seems unlikely that they contribute to the initial seeding of human epidermis with Langerhans cells. Because they do not express CD14, it also seems unlikely that they correspond to the monocyte precursors in the first phase of Langerhans cell repopulation in inflamed murine epidermis. In contrast, the cytokines supporting human CD1c⁺ DC conversion into Langerhans cells are all epithelial cell derived, and the Langerhans cell progeny express skin-homing receptors. CD1c⁺ DCs are therefore plausible candidate precursors responsible for the second phase of epidermal repopulation by Langerhans cells after an inflammatory insult.

The identification of a phenotypically defined Langerhans cell precursor in blood could provide a more exportable methodology for generating this highly potent DC subtype in vitro, rather than the current standard methodology of starting with CD34⁺ hematopoietic progenitor cells. To this end, however, more rigorous side-by-side functional rather than phenotypic comparisons are required between different candidate Langerhans cells. Although technically and logistically demanding, Langerhans cells isolated from the epidermis will remain the “gold standard.”

Human Langerhans cells are the most potent DC subtype for the stimulation of CTLs, which they accomplish without interleukin-12p70; human Langerhans cells are the most potent cross-presenting DC subtype. In this respect, the 2 studies discussed here present investigators with some unresolved paradoxes. Martinez-Cingolani et al describe a Th2 profile stimulated by their Langerhans cells progeny, which would not support potent CD8⁺ CTL generation. Moreover, because CD14⁺ (BDCA-3⁺) and CD1c⁺ (BDCA1⁺) mark mutually exclusive DC subsets, in which CD14⁺ (BDCA3⁺) DCs are the most potent cross-presenting DCs, then both Milne et al.
and Martínez-Cingolani et al present investigators with another ambiguity. Absent functional data, it remains unclear how they would reconcile the BDCA-1+/CD1c+(BDCA-3−/CD141−) profile of the DC precursors they describe with the resultant Langerhans cell progeny that should have potent cross-presenting capacity, nominally associated with the converse CD141+ (BDCA3−) phenotype. Detailed functional data will again therefore prove essential in extending these groups’ very compelling and novel findings.

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REFERENCES


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Mutations of ETNK1 in aCML and CMML

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In this issue of Blood, Gambacorti-Passerini et al describe, for the first time, mutations of an ethanolamine kinase called ETNK1, which is physiologically involved in the first step of the phosphatidylethanolamine biosynthesis pathway. The authors describe 2 recurrent point mutations of ETNK1 in 9% of atypical chronic myeloid leukemias (aCMLs) and show that these mutations are associated with the impaired catalytic activity of the kinase.

A typical CML is an entity defined in the World Health Organization 2008 classification that belongs to the group of myeloproliferative/myelodysplastic disorders. Since 2013, next-generation sequencing approaches conducted on aCML patient samples have described recurrent mutations in CSF3R and SETBP1, genes whose mutations are able to activate cellular proliferation.

Long known in oncogenesis, the activating mutations of the granulocyte colony-stimulating factor receptor, also called CSF3R, were first described in 25% to 50% of aCML cases as well as in 3% of chronic myelomonocytic leukemia (CMML) cases in 2013. In aCML, a hot spot affecting codon 618 is frequently affected and could be a therapeutic target in response either to Src kinase or to Janus kinase inhibitors.

Initially described in more than 90% of patients with Schinzel-Giedion syndrome, SETBP1 mutations were identified in 24.3% of aCML samples tested by Piazza et al. At the same time, SETBP1 mutations have been identified in other hematological malignancies, specifically in 4% to 14% of CMMLs, demonstrating one more time that the mutational spectrum between aCML and CMML is very close. SETBP1 mutations were characterized as conferring a proliferative advantage to mutated cells and as closely related to a negative effect on overall survival in patients with aCML. As suggested by Makishima et al, the presence of SETBP1 mutations could allow the use of transforming...
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