Interleukin-33 at Epidermal and Endothelial Barriers in Humans

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Olav Sundnes, who is a dermatology resident at the Oslo University Hospital, defended his thesis on March 31, 2017, titled «Interleukin-33 at human epidermal and endothial barriers» for the degree of PhD at the University of Oslo. Main supervisors were Guttorm Haraldsen and Denis Khnykin.

'Alarmins' are endogenous molecules that are constitutively available and, when released upon cell death or damage, activates the immune system. These alarm signals are thus likely the most proximal mediators of inflammatory responses after tissue damage. Interleukin-33 (IL-33) is a novel IL-1 family member and putative alarmin thought to have broad effects on the immune system. However, most of our knowledge of this molecule is based on animal models. The aim of this thesis was therefore to investigate the biology of human IL-33 with a special focus on the human epidermis and endothelium.

In the first part of the thesis, using carefully validated immunohistochemistry, we defined the expression of IL-33 in human skin where endothelial cells were the main IL-33 reservoirs in healthy homeostasis (1). Keratinocytes did not show constitutive expression, but instead strongly upregulated IL-33 during the inflammatory setting of experimentally induced wound healing. This pattern of expression was markedly different from murine skin, thus identifying potentially important species differences.

We also characterized distinct modes of regulation of IL-33 in human keratinocytes, confirmed in skin organ cultures, including a novel mechanism of IL-33 induction by hypoosmotic stress (2). Importantly, IL-33 showed nuclear localization in all settings, with no evidence of active release.

To investigate the behaviour of IL-33 as an alarmin *in vivo*, we analysed serially collected blood samples from trauma patients, and were for the first time able to confirm systemic release of human IL-33 after tissue damage (3). Finally, we studied the effect of extracellular IL-33 on endothelial cells, finding that

only nonquiescent cell responds due to a novel regulation mechanism of the IL-33 receptor (4).

The studies provide new insight into the biology of human IL-33 and will hopefully contribute to a better understanding of the role of IL-33 in human disease.

List of original publications

1. Sundnes O, Pietka W, Loos T, Sponheim J, Rankin AL, Pflanz S, et al. Epidermal Expression and Regulation of Interleukin-33 during Homeostasis and Inflammation: Strong Species Differences. J Invest Dermatol 2015; 135: 1–10.
2. Sundnes O, Pietka W, Bertelsen V, Stav-Noraas T-E, Galtung HK, Khnukin D, et al. Hypoosmotic stress drives IL-33 production in human keratinocytes – a novel epidermal stress response. Manuscript.
3. Sundnes O, Ottestad W, Schjalm C, la Cour Poulsen L, Mollnes TE, Haraldsen G, et al. IL-33 is rapidly released to the systemic circulation during severe trauma in humans. Manuscript.
4. Pollheimer J, Bodin J, Sundnes O, Edelmann RJ, Skånland SS, Sponheim J, et al. Interleukin-33 drives a proinflammatory endothelial activation that selectively targets nonquiescent cells. Arterioscler Thromb Vasc Biol 2013; 33: e47–55.