



NSI Meeting Announcement

Date: Thursday, October 30th, 12:15 – 13:00

Venue: Seminar room A3.3067, Rikshospitalet

Double lecture

By

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Intranuclear cytokines and alarmins in host defence

Several cytokines act not only as secreted auto- or paracrine proteins but also as nuclear messengers in an “intracrine”, nonsecreted manner. The intracellular accumulation of cytokines may have represented an evolutionary advantage, because readily secreted proteins in aquatic life forms would be unable to function during regenerative processes. The evolution of extracellular receptors appears to have brought a duality of cytokine function, as they are thought to regulate transcription but also to constitute a pool of inflammatory cytokines that can be released in association with cellular damage. For example, HMGB1 (high-mobility group protein B1) is an abundant nuclear protein tightly associated with chromatin folding but once released is thought to act as an “alarmin” and bind to toll-like receptors (TLRs) 2, 4, and 9 and RAGE (receptor for advanced glycation end-products). Likewise, interleukin-1 α is targeted to the nucleus and thought to facilitate proinflammatory activation, but also to be released from damaged cells. The latest addition to this list of “intrakines” appears to be interleukin-33, a recently discovered member of the interleukin-1 family. In its secreted form IL-33 binds the ST2 receptor and activates Th2 lymphocytes, eosinophils and mastcells, but in healthy tissues it appears that vascular endothelial cell nuclei may be a major reservoir. Moreover, nuclear IL-33 appears to act as a transcriptional repressor, perhaps by controlling nucleosome compaction via histone interaction.

Intranuclear IL-33 and endothelial cell activation

Interleukin (IL)-33 is a novel member of the IL-1 family of cytokines that promotes Th2 responses in lymphocytes as well as the activation of both mast cells and eosinophils via the ST2 receptor. Additionally, IL-33 has been proposed to act as a chromatin-associated transcriptional regulator in both endothelial cells of high endothelial venules and chronically inflamed vessels. We now demonstrate that nuclear IL-33 is expressed in blood vessels of healthy tissues but down-regulated at the earliest onset of angiogenesis during wound healing; in addition, it is almost undetectable in human tumor vessels. Accordingly, IL-33 is induced when cultured endothelial cells reach confluence and stop proliferating but is lost when these cells begin to migrate. Activation of endothelial cell cultures with either tumor necrosis factor- α or vascular endothelial growth factor and subcutaneous injection of these cytokines led to a down-regulation of vascular IL-33, a response consistent with both its rapid down-regulation in wound healing and loss in tumor endothelium. In conclusion, we speculate that the proposed transcriptional repressor function of IL-33 may be involved in the control of endothelial cell activation.

Refreshments will be served from 12:00

Welcome all!



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