

**Presentation:**

Cellular and Extracellular Endogenous Agonists

**Speaker:**

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**Abstract:**

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The toll-like receptors (TLR) monitor for pathogenic microorganisms and excite responses that contain and eradicate those organisms that invade the body. Once thought to recognize predominantly microbial substances, toll-like receptors also excite responses against organisms lacking stimulatory substances and may activate these responses in "sterile conditions" such as the systemic inflammatory response syndrome in which microorganisms are absent. Accordingly, we sought endogenous agonists that activate toll-like receptors. We found that the TLR-4 can be stimulated by heparan sulfate, a component of cell surfaces and extracellular matrices, and that enzymes that liberate heparan sulfate enable recognition of the endogenous agonist to proceed. Since TLR-4 and its agonist are present in the same place at the same time, we reasoned that the function of TLR-4 must be tightly controlled. Consistent with this concept, we found that cells bearing TLR-4 studied in a model of the tissue microenvironment and cells in whole animals signal poorly when stimulated with pure agonist but signal vigorously when the receptors are "released from suppression" by the action of proteases. The same enzyme that releases suppression can in larger amounts solublize endogenous agonists. This mechanism of endogenous activation and control may explain both the response to infection and the involvement of TLR-4 in sterile conditions such as the systemic inflammatory response syndrome, atherosclerosis and osteoporosis.