Resistin is a modulator of inflammation and autoimmunity

Akademisk avhandling

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Av Elisabeth Almer Boström

Fakultetsopponent: Professor Roland Jonsson
The Gade Institute, University of Bergen, Norway

Avhandlingen baseras på följande delarbeten:

I

Bostrom EA, Forsblad D'Elia, Dahlgren U, Simark-Mattsson C, Hasséus B, Carlsten H, Tarkowski A, Bokarewa M

Salivary resistin reflects local inflammation in Sjögren's Syndrome
J. Rheumatology, 2008 Oct;35(10):2005-11.

II

Bostrom EA, Ekstedt M, Kechagias S, Sjöwall C, Bokarewa M, Almer SH

Resistin is elevated in autoimmune disease of the gastrointestinal tract reflecting ANA positivity
Submitted

III

Bostrom EA, Tarkowski A, Bokarewa M

Resistin is stored in neutrophil granules being released upon challenge with inflammatory stimuli
Biochim Biophys Acta. 2009 Sep 18

IV

Bostrom EA, Andersson S, Gustafson B, Ekwall AK, Eisler, T, Dahlberg L, Smith U, Bokarewa M

Resistin and insulin/insulin-like growth factor signalling in rheumatoid arthritis
Manuscript

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Abstract

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Resistin is a protein with proinflammatory properties in man and a regulator of glucose metabolism in mice. Human resistin activates the nuclear factor kappa-B dependent cytokine cascade; however, its full role in inflammation in terms of regulation, expression, and cellular source is not entirely understood. Resistin may have a role in insulin growth factor signaling. The main aim of this thesis was to investigate the role of resistin in inflammation, with emphasis on rheumatic diseases and diseases of the liver and gastrointestinal tract; in addition, the neutrophil was evaluated as a possible source of resistin. Another aim was to investigate the effect of resistin on IGF signaling in a new mouse model of arthritis.

In paper I, resistin was shown to be associated with local inflammation in patients with primary Sjögren's syndrome. This conclusion was based on the finding of elevated resistin levels in saliva and in the salivary gland tissue of patients. Moreover, resistin levels were significantly higher in patients with high focal infiltration of leukocytes in glandular tissue than in those with no or low leukocyte infiltration. In paper II, resistin levels were found to be elevated in a wide variety of inflammatory and autoimmune conditions of the liver and gastrointestinal tract. Furthermore, they were significantly higher in patients who were seropositive for anti-nuclear antibodies than those who were seronegative. In paper III, a new cell source of resistin in inflammation was identified, namely the neutrophil. Subcellular fractionation of the neutrophil confirmed the presence of resistin in the azurophil granules and the specific granules. In a rheumatoid arthritis (RA) model in paper IV, resistin was shown to modulate IGF signaling. Levels of IGF-1 were significantly lower in RA patients, especially those with systemic inflammation, than in controls with non-inflammatory joint conditions, and they were inversely related to resistin levels. Resistin expression was abrogated in a transplantation mouse model of RA synovia. This led to downregulation of IGF-1R expression and intracellular Akt activity.

Taken together, these results indicate that resistin is an immunomodulatory molecule that is expressed locally at the site of inflammation. It is produced by neutrophils and possibly modulates IGF signaling. These findings suggest that resistin regulates both inflammation and could affect growth factor-related signaling in humans.

Key words: Resistin, inflammation, autoimmunity, rheumatoid arthritis, Sjögren's syndrome.

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