Influence of the adenosine/A2A receptor and TG2 on the inflammatory response of macrophages

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Multicellular organisms respond to bacterial and fungal infection with the complex biological program of inflammation. In the initial phase of inflammation, macrophages and neutrophil granulocytes migrate to the site of infection, where they not only phagocytose pathogens, but also recruit further immune cells and induce systemic inflammatory response by the production and release of pro-inflammatory cytokines. In the resolution phase of inflammation, macrophages remove neutrohils, which died during their action. The uptake of these apoptotic cells induces phenotype shift: macrophages pass into deactivated phase, in which they release anti-inflammatory cytokine TGF-β and IL-10 instead of pro-inflammatory mediators.

In the present study we reported, that the lack of TG2 affects the inflammatory answer of macrophages, as TG2 null macrophages respond to LPS treatment by elevated IL-6 and TNF-α production. Though TGF-β has been proposed to act as a negative feed back regulator of pro-inflammatory cytokine production in LPS-stimulated macrophages, this phenomenon is not related to the lack of active TGF-β production. Instead, in the absence of TG2 integrin β3 maintains an elevated basal Src family kinase activity in macrophages, which leads to enhanced phosphorylation and degradation of the IκBα. Low basal levels of IκBα explain the enhanced sensitivity of TG2 null macrophages to signals that regulate NF-κB-mediated pro-inflammatory cytokine production. Our data suggest that TG2 null macrophages bear a proinflammatory phenotype, which might contribute to the enhanced susceptibility of these mice to develop autoimmunity and atherosclerosis.

In addition to TGF-β, macrophages engulfing apoptotic cells release adenosine in sufficient amount to trigger A2ARs, and simultaneously increase the expression of A2ARs, as a result

of possible activation of LXR and PPARδ. In macrophages engulfing apoptotic cells, stimulation of A2ARs suppresses the NO-dependent formation of neutrophil migration factors, such as MIP-2, using the adenylate cyclase/PKA pathway. As a result, loss of A2ARs results in elevated chemoattractant secretion. This was evident as pronounced neutrophil migration upon exposure of macrophages to apoptotic cells in an in vivo peritonitis model. Altogether, our data indicate that adenosine is one of the soluble mediators released by macrophages that mediate engulfment-dependent apoptotic cell suppression of inflammation, and TG2 is anti-inflammatory by both promoting active TGF-β formation and regulating integrin signaling.

Keywords: tissue transglutaminase; integrin αvβ3; adenosine; A2A receptor;

Kulcsszavak: szöveti transzglutamináz, integrin αvβ3; adenozin; A2A receptor;