Spatiotemporal regulation of Toll-like receptors and RAGE signaling pathways by S100B protein restrains inflammation

Guglielmo Sorci, Gloria Giovannini, Francesca Riuzzi, Pierluigi Bonifazi, Teresa Zelante, Silvia Zagarella, Francesco Bistoni, Rosario Donato, Luigina Romani

Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Italy

The Ca^{2+}-binding protein of the EF-hand type, S100B, exerts intracellular and extracellular activities by altering the functions of several intracellular target proteins and engaging the receptor for advanced glycation end-products (RAGE) in responsive cells, respectively [1]. In the latter case, S100B was shown to exert either pro-survival, mitogenic and differentiation-promoting or pro-apoptotic, proinflammatory and anti-differentiation effects depending on its concentration, the cell type and the context [1]. Due to its pro-inflammatory activity under certain conditions, S100B has been proposed to act as a danger signal, i.e. a factor that is released by damaged tissues and regulates the inflammatory response. Humans inhale hundreds of *Aspergillus conidia* per day without adverse consequences. Powerful protective mechanisms may ensure prompt control of the pathogen and resolution of inflammation before collateral tissue injury. Here we reveal a previously unknown mechanism by which a "danger-sensing" mechanism stopped overactive pathogen-induced immune cell activation and ensured tissue protection. This occurs through RAGE-dependent inhibition of Toll-like receptor 2 (TLR-2) signaling and NF-κB activation. We observed an increased susceptibility to *Aspergillus*-induced inflammation in the absence of RAGE. Mechanistically, TLR-2 activation by the fungus resulted in the release of S100B from bronchial epithelial cells, that mediated the activation of RAGE on neutrophils, and in RAGE association with TLR2 and subsequent TLR-2 inhibition. However, S100B-induced inflammation through sustained RAGE activation also occurred in infection in the relative absence of TLRs acting through a nucleic acid-sensing mechanism inhibiting S100B via NF-κB activation. Thus, the spatiotemporal regulation of TLRs and RAGE by S100B limits pathogen- as well as danger-induced inflammation and provide evidence for an evolving braking circuit in infection whereby an endogenous danger signal protects against pathogen-induced inflammation and a pathogen-sensing mechanism resolves danger-induced inflammation.

Reference

[1] Donato R et al. (2009) Biochim Biophys Acta 1793: 1008-1022.

Key words
S100B, RAGE, aspergillosis, TLRs, PAMP, DAMP