RAGE and TLRs: Relatives, friends or neighbours?

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ABSTRACT

The innate immune system forms the first line of defense against infectious and non-infectious tissue injury. Cells of the innate immune system detect pathogen-associated molecular patterns or endogenous molecules released as a result of tissue injury or inflammation through various innate immune receptors, collectively termed pattern-recognition receptors. Members of the Toll-like receptor (TLR) family of pattern-recognition receptors have well established roles in the host immune response to infection, while the receptor for advanced glycation end products (RAGE) is a pattern-recognition receptor predominantly involved in the recognition of endogenous molecules released in the context of infection, physiological stress or chronic inflammation. RAGE and TLRs share common ligands and signaling pathways, and accumulating evidence points towards their co-operative interaction in the host immune response. At present however, little is known about the mechanisms that result in TLR versus RAGE signalling or RAGE-TLR cross-talk in response to their shared ligands. Here we review what is known in relation to the physico-chemical basis of ligand interactions between TLRs and RAGE, focusing on three shared ligands of these receptors: HMGBl, S100A8/A9 and LPS. Our aim is to discuss what is known about differential ligand interactions with RAGE and TLRs and to highlight important areas for further investigation so that we may better understand the role of these receptors and their relationship in host defense.

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1. Introduction

RAGE and TLRs play a critical role in the innate immune system as they can recognize and interact with microbial products (i.e. pathogen-associated molecular patterns or PAMPs) as well as endogenous molecules released in the context of tissue injury and inflammation (i.e. damage-associated molecular patterns or DAMPs). Ligation of RAGE and TLR signalling results in the activation of immune and inflammatory responses involved in host defence (Botos et al., 2011; Chang, 2010).

Recently, it has been suggested that RAGE and some members of the TLR family functionally interact to coordinate and regulate immune and inflammatory responses. RAGE co-operation with certain TLRs results in amplification of inflammatory responses and there is increasing evidence to support their potential synergism.

RAGE and TLRs share several common ligands including HMGBl (Hori et al., 1995; Huttunen et al., 2002; Ivanov et al., 2007; Jordon and Eddokia, 2012; Liu et al., 2009; Park et al., 2014; Yang et al., 2010a; Yang et al., 2012), the S100A8/A9 heterodimeric protein complex (Turovskaia et al., 2008; Vogl, 2007), the bacterial cell wall component LPS (Visintin et al., 2003; Yamamoto et al., 2011) and β-sheet fibrils like serum amyloid A (Cheng et al., 2008; Yan et al., 2000) and amyloid β (Deane et al., 2003; Iddan et al., 2008; Yan et al., 1996; Yan et al., 1998). RAGE also appears to interact with TIRAP and MyD88, both of which are intracellular adaptor proteins used by TLRs to activate downstream signalling pathways (Hreggvidsdottir et al., 2009; Ivanov et al., 2007; Qin et al., 2009; Sakaguchi et al., 2011; Tian et al., 2007).

So far, much of the evidence in the literature relating to RAGE and TLR co-operation or synergy has focused on signalling pathways downstream of these receptors and the outcome of these interactions on the inflammatory response. However, understanding of the mechanism of RAGE-TLR cross-talk at the receptor level is extremely limited and important questions remain to be addressed – particularly whether RAGE–TLR synergy is due to physical association of the receptors. Here we discuss what is known about the structural and biochemical basis of ligand interactions with RAGE and TLRs, with a view to highlighting possible mechanisms of RAGE and TLR co-operation at the receptor level.