

THE ACTIVATION OF THE RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (RAGE) CONTRIBUTES TO THE INDUCTION OF HDM-SPECIFIC T_H2 RESPONSES

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The receptor for advanced glycation end products (RAGE) is a pattern-recognition receptor (PRR) which interacts with a diverse repertoire of endogenous ligands involved in the host immune response to injury, infection and chronic inflammation. RAGE can function as a molecular platform for the recognition of various ligand complexes via its collaboration with other PRRs including TLR4. Since TLR4 has been shown to be crucially involved in the airway response to inhaled allergens, we investigated whether RAGE contributes to the development of allergic airway inflammation in an animal model of asthma. Intranasal sensitization and challenge with house dust mite (HDM) resulted in the translocation of the RAGE ligand HMGB1 from the nucleus to the cytoplasm in both wild-type (WT) and RAGE-deficient (RAGE^{-/-}) mice. In the absence of RAGE, gene expression of T_H2 and T_H17 cytokines in the lung was attenuated. In addition, draining lymph node cells cultured from RAGE^{-/-} mice produced significantly less HDM-specific IL-5 and IL-17A. RAGE^{-/-} mice were protected against eosinophilic inflammation, but had a more pronounced neutrophilic response, despite reduced expression of pro-neutrophilic cytokines and chemokines (IL-17A, CXCL1, CXCL2, CCL3). These findings provide the first evidence that RAGE contributes to the development of T_H2- and T_H17-associated allergic airway inflammation. Further studies interrogating the mechanisms by which RAGE mediates the allergic inflammatory response; particularly as to whether this involves direct recognition/interaction with allergenic proteins, and/or occurs secondary to the release of endogenous RAGE ligands, and the co-requirement for TLR4 signalling, may expose new pathogenic processes that promote the onset of asthma.

Conflict of interest: No