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PReS-FINAL-2182: The role of murine rage in innate immune responses and inflammation: a systematic approach

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Introduction

The receptor for advanced glycation end products (RAGE) is a multi-ligand receptor expressed on various cells which interacts with a diverse class of ligands, e.g. 'danger signals' such as neutrophil-derived S100A12. RAGE has been implicated in the pathogenicity of various inflammatory diseases. However, the exact role of RAGE has not been sufficiently defined. Our recent data on S100A12-induced activation of monocytes points to a modulatory rather than pro-inflammatory function of human RAGE.

Objectives

To assess the role of RAGE in a more systematic way, we generated RAGE-/- mice and analyzed immune cell functions *in vitro*, followed by murine models of *staphylococcus aureus* infection (dermal immunity), chemically induced colitis (mucosal immunity), lethal inflammatory liver injury (septic shock) and collagen induced arthritis (autoimmunity) comparing RAGE-/- and C57BL/6 wild-type (wt) mice.

Methods

Reactive oxygen species (ROS) production, phagocytosis and cytokine production of bone marrow derived monocytes were measured using flow cytometry. *Staphylococcus aureus* (*S. aureus)* infection was induced by footpad injection. Acute and chronic colitis were induced chemically by dextran sodium sulfate (DSS) solution. For the inflammatory liver injury model, mice were challenged with D-galactosamine (D-Gal) along with lipopolysaccharide (LPS). Arthritis was induced by injection of heterologous type II collagen (CII).

Results

We observed no differences of cellular immune function (ROS and cytokine production, phagocytosis) in RAGE-/- compared to wt monocytes. Male, but not female RAGE-/- mice showed more footpad swelling and bacterial dissemination in the *S. aureus* infection model. In the DSS colitis model we observed no significant differences between the two strains, whereas RAGE-/- mice were significantly protected from lethal D-Gal/LPS induced liver injury. RAGE-/- and wt mice develop arthritis at similar clinical scores and incidence with no detectable differences in type II collagen autoantibody levels. However, in female animals there is a strong tendency towards aggravated disease, less remission and higher disease penetrance.

Conclusion

Overall, the contribution of RAGE seems to largely depend on the disease model and cell type studied. While no overall differences with respect to immune cell activities were observed, a striking gender specific effect of RAGE seems to be involved in some conditions.

Disclosure of interest

None declared.

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