Cell Communication and Signaling BioMed Central

Meeting abstract

Open Access

Human S100A8 and S100A9 activate phagocytes via Toll-like receptor 4 independent of RAGE

T Vogl*[1], M Wolf[1], B Petersen[1], C Ehrhardt[2], MAD van Zoelen[3], D Foell[1] and J Roth[1]

Address: [1]Institute of Immunology, University of Münster, Münster, Germany, [2]Institute of Molecular Virology, University of Münster, Münster, Germany and [3]Center of Infection and Immunity Amsterdam, University of Amsterdam, The Netherlands

* Corresponding author

from 12th Joint Meeting of the Signal Transduction Society (STS). Signal Transduction: Receptors, Mediators and Genes
Weimar, Germany. 29–31 October 2008

Published: 26 February 2009

Cell Communication and Signaling 2009, **7**(Suppl 1):A91 doi:10.1186/1478-811X-7-S1-A91

This abstract is available from: http://www.biosignaling.com/content/7/S1/A91

Endogenous Damage Associated Molecular Pattern (DAMP) proteins are known as important pro-inflammatory factors of the immune system, which are released during cellular stress. Recognition of DAMPs involves the multiligand Receptor for Advanced Glycation End products (RAGE) and Toll-like receptors (TLRs) in sensing not only Pathogen Associated Molecular Patterns (PAMPs) but also endogenous proteins. Members of the fast growing family of DAMP proteins are besides heat shock proteins, HMGB1 or defensins also some members of the family of S100 proteins, which promote inflammatory processes. It was claimed that RAGE is involved in almost all S100 protein activities.

We here investigated the capacity of human S100A8 (MRP8, myeloid related protein 8) and human S100A9 (MRP14) on activation of human phagocytes. S100A8 and S100A9 form homodimers as well as heterodimers and belong to the S100 family of EF-hand calcium-binding proteins. Both proteins are the major cytoplasmic proteins of phagocytes and are released at sites of inflammation by activated or necrotic phagocytes.

While human S100A8/S100A9-complexes did not show any phagocyte activation, S100A8 homodimers as well as S100A9 homodimers induce strong pro-inflammatory mechanisms in these cells. Human S100A9 induces intracellular translocation of MyD88 and activation of IRAK-1 as shown recently already for murine S100A8. Finally NF-kB activation results in elevated expression of TNF-alpha as well as other pro-inflammatory genes. In blocking experiments with TLR4-specific monoclonal antibodies we demonstrate that both S100 proteins specifically signals via TLR4 receptor complex on human phagocytes. Using TLR4/MD2/CD14 transfected HEK293 cells and RAGE transfected HEK293 cells we clearly can exclude the involvement of RAGE for at least these two S100 proteins.

Our *in vitro* results could be further confirmed in vivo. Mice lacking S100A8/S100A9 are protected against abdominal sepsis induced by E. coli. Our present data clearly demonstrate the importance of TLR4 by which phagocytes promote their own activation via expression and secretion of endogenous ligands of this receptor.