Vascular effects of M1 protein from *Streptococcus pyogenes*: 
Implications for the pathophysiology of sepsis

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**Background:**
Sepsis is a devastating condition in which a dysregulated host response to an infection may lead to multiple organ failure. The mortality in sepsis and septic shock is high, at least 25%. *Streptococcus pyogenes*, a Gram-positive bacterium which may cause sepsis, expresses surface bound M proteins. There are more than 200 different M protein serotypes. Among these, *S. pyogenes* strains of the M1 serotype are among the most prevalent in cases of severe invasive infections such as sepsis. M1 protein interacts with the host, for example via anti-phagocytic properties and triggering monocytes to release cytokines. However, it is not very well known how M proteins effects the vascular wall directly, which is an important piece of the understanding of the development of hypotension in sepsis.

**Materials and methods:**
In study no. 1 we incubated rat aorta segments with M1 protein and measured the contractile response to phenylephrine, a vasoconstrictor. We measured release of nitrite/nitrate (products of NO), investigated involvement of toll like receptors and co-localization with M1 on the vascular cell surfaces of knock-out mice.

In study no. 2 similar experiments were performed on human omental arteries, and the influence of plasma, fibrinogen, immunoglobulin G and albumin was studied. Determination of cytokine release into medium was done after 48 h incubation.

**Main results:**
Blood vessels incubated with M1 protein respond weaker to vasoconstrictors, in the human vessels only after incubation in the presence of plasma. NO release from rat aorta was significantly higher after incubation with M1 protein compared to control, but this effect was not seen in human arteries. Human vessels produced significantly higher levels of the inflammatory cytokines IL-6 and IL-8, when plasma or fibrinogen were present with M1 protein.

**Importance:**
We need to understand the bio-molecular mechanisms in order to improve outcome of sepsis patients. Antibiotic therapy is not enough, and other molecular paths needs to be
further explored. My studies show a direct effect of M1 protein from *Streptococcus pyogenes* on blood vessels, which can guide future development of targeted therapy.

Publications:

“M1 protein from *Streptococcus pyogenes* induces nitric oxide-mediated vascular hyporesponsiveness to phenylephrine: involvement of Toll-like receptor activation”

Thorgerdur Sigurdardottir, Viveka Björck, Heiko Herwald, Matthias Mörgelin, Sigurbjörg Rutardottir, Johan Törnebrant, and Mikael Bodelsson. Shock: 2010

“Streptococcal M1 protein induces hyporesponsiveness and cytokine release from human arteries in a fibrinogen-dependent manner: A translational study”

Viveka Björck, Lisa I. Påhlman, Johan Törnebrant, and Mikael Bodelsson

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