Inflammatory Mediators and Coagulation in Sepsis

Why do patients with infections mount an inflammatory response that produces the clinical syndromes of sepsis and septic shock?

The answer is complex and poorly covered in textbooks so you will have stay awake in the lecture to find out! Much research over the last 20 years has defined the mechanisms that produce human sepsis quite well. These studies have also been important as they have shown potential targets for novel therapeutic interventions in sepsis that are beginning to show clinical benefit.

The key to understanding the complex mediators in sepsis is to break down the syndrome into 3 key steps.

1. **Bacterial products that trigger the sepsis syndrome.**
   Humans are “pre-programmed” to recognise invasion by microbes. This is part of what is called the innate immune system. We have evolved a number of recognition pathways for common components of bacteria that signal we have been invaded by a pathogen.

   Important bacterial components are:
   - Lipopolysaccharide
   - Flagellin
   - Lipoteichoic acid

   We will discuss some of the key structural features of bacteria and the host receptors that allow us to recognise them.

2. **The immediate host response to these bacterial components**

   The goal of any host response to invasion with microbes is to limit their spread and if possible kill them. The immediate host response is thus to produce mediators that will for example attract phagocytes and make them more able to kill microbes. Blood flow to the infected part of the body will increase to allow phagocytes, complement and antibodies to reach the invaders. Most of these effects are produced by proteins called cytokines that are released following infection. We will discuss three important cytokines: interleukin-1, tumour necrosis factor and interferon-gamma.

3. **Downstream Effects of Cytokines**

   Cytokines induce a range of effects in the body. We will consider the production of nitric oxide, a key mammalian mediator that is responsible for the hypotension of septic shock. We will also consider the effects that cytokines and bacterial products have upon blood coagulation. If you are anything like me, I find the coagulation cascade very difficult to remember so I have set out below a diagram showing the important pathways involved:
We will discuss in the lecture how sepsis results in activation of the extrinsic pathway through the production of tissue factor and how the natural anti-thrombotic pathways - that usually control blood clotting - are altered in sepsis. The important anti-thrombotic pathway is that produced by a protein called Protein C. Activation of protein C not only helps prevent excessive blood coagulation but it also damps down the inflammatory response. Activation of protein C is defective in sepsis resulting in inappropriate blood coagulation leading to poor organ perfusion and organ failure. In addition, the inflammatory response is left to go unchecked.