Adverse effects of therapeutic plasma protein preparations

Detection of activated coagulation factors

Therapeutic concentrates of coagulation factors, immunoglobulins or albumin should contain exclusively native proteins, but neither activated factors, nor any other contaminating proteolytic activity. This is an important matter of safety (e.g. thrombogenicity). Thus, the search for such activities is an important element during batch release. We develop ultra-sensitive assays for the identification of activated factors.

In a prothrombin complex concentrate (PCC) we could identify prothrombin overload as major thrombogenic factor (Dusel et al. 2004).

In 2010 an increased incidence of thromboembolic complications was observed after administration of 5% intravenous immunoglobulins, leading to the suspension of the manufacturing license of the concerned product. Investigations on the causative agent using specific activity assays and inhibitors, and applying a thrombin generation assay identified significantly elevated level of FXIa as the most likely cause for the thrombogenic potential in concerned lots of this product (Grundmann et al. 2010; Etscheid et al., 2012). These findings and similar observations from other research groups lead to a revision in the monograph for immunoglobulins (Ph. Eur. 01/2012:0918). Elimination of any thrombosis-generating agents and the identification of activated coagulation factors, their zymogens and process steps that may cause their activation became mandatory for the production process of intravenous immunoglobulins.

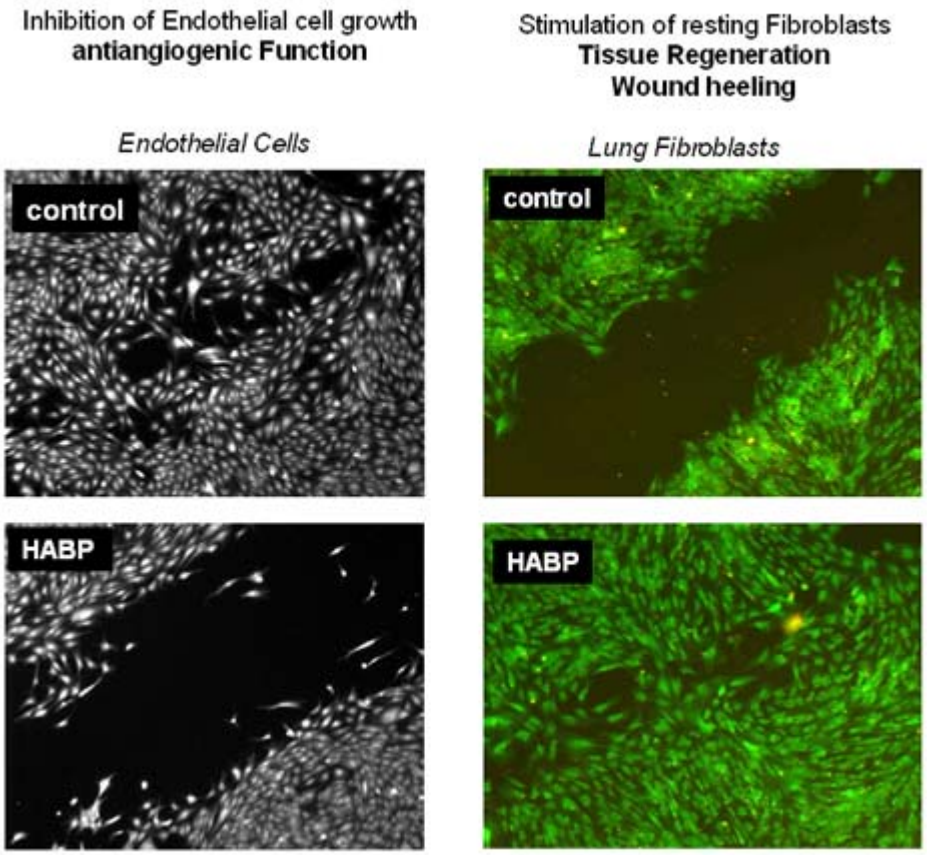
Drug-related blood cell activation

An in-depth analysis of the above mentioned thromboembolic complications showed that not only FXIa, but also mediators which in vitro triggered an activation of platelets or other blood cells were contained in the product (Salge-Bartels et al. 2014). Detailed analysis is performed to reveal the mechanisms and possibly the agonists in order to improve the product safety.

Functional characterisation of the plasma protease FSAP

During batch release of prothrombin complex concentrates, we found a proteolytic activity which was related to a novel plasma proenzyme (Hunfeld et al. 1999). Amino acid sequencing showed high homology with a hyaluronan-binding protein which had recently been described, albeit in a different context. The protein was tentatively named as hyaluronan-binding protease (HABP), and is now most commonly known as Factor VII-activating protease (FSAP).

Supported by a grant of the Bundesministerium für Gesundheit (BMG), we have evaluated the impact of FSAP on the quality of blood products, and characterised the physiological function. The proenzyme becomes activated by autoactivation, and can activate Factor VII and prourokinase. Our experiments showed an involvement in contact activation and differential actions on various cells, including antiangiogenic activities or activation of signalling pathways that trigger cell growth and migration, important processes in tissue regeneration and wound healing (Etscheid et al. 2007). In cooperation with the University of Gießen it was shown that FSAP accelerates the extrinsic pathway of coagulation by inactivation of a major regulator of extrinsic coagulation, tissue factor pathway inhibitor (TFPI). Consequently, we currently explore the physiological and pathophysiological impact of these findings in in vivo models, with particular emphasis on thrombosis and haemostasis.



Inhibition of Endothelial cell growth antiangiogenic Function - Stimulation of resting Fibrolasts: Tissue Regeneration Wound heeling. Source: PEI