**Activity 3 – Coagulation**

A thrombus composed of platelets is neither secure nor strong enough to prevent blood loss following vessel injury. A further biochemical process known as coagulation occurs to strengthen the platelet thrombus. Coagulation results in the formation of a fibrin network that enmeshes and stabilises a growing thrombus. Feedback reactions are also triggered by coagulation that further activates platelets, ensuring that a large thrombus is formed that will prevent blood loss.

**Coagulation Factors and the Coagulation Cascade**

Coagulation is a cascade of activity of a number of blood enzymes called Factors (see table below). Enzymes are able to alter a substrate without undergoing any change themselves, so are able to perform many individual reactions. This is useful in coagulation where a small initial event results in an amplification of a response by progressive rounds of enzyme activity. Coagulation factors are generally serine proteases (so called because they have a serine in the active site). They are inactive in the blood, but become active on injury to the vessel wall.

**Coagulation Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Common name</th>
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<tbody>
<tr>
<td>Factor I</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Factor II</td>
<td>Prothrombin</td>
</tr>
<tr>
<td>Factor III</td>
<td>Tissue Factor</td>
</tr>
<tr>
<td>Factor V</td>
<td>Proaccelerin</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Proconvertin</td>
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<tr>
<td>Factor VIII</td>
<td>Antihaemophilic Factor A</td>
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<tr>
<td>Factor IX</td>
<td>Christmas Factor</td>
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<tr>
<td>Factor X</td>
<td>Stuart-Prower Factor</td>
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<tr>
<td>Factor XI</td>
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<tr>
<td>Factor XII</td>
<td>Hageman Factor</td>
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<tr>
<td>Factor XIII</td>
<td>Fibrin stabilising factor</td>
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<tr>
<td>Prekallikrein</td>
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</tbody>
</table>
Q. Coagulation Factors and Disease - what are the main types of haemophilia?

There are two pathways of coagulation, the Intrinsic (Contact) pathway and the Extrinsic (Tissue factor) pathway. Both pathways are activated following injury to the vessel wall, and although they have different mechanisms of initiation and components, they both converge at a common point. Coagulation consists of a series of enzymatic reactions, with one enzyme activating the subsequent downstream enzyme. Activation occurs by proteolysis (one factor digests a part of an inactive factor, resulting in its activation). As enzymes are unaffected by their action, this can lead to a rapid increase in activity along the pathways, generating large amounts of fibrin.

Extrinsic pathway

In the extrinsic pathway, Tissue Factor (Factor III) present in the sub-endothelial tissues becomes exposed by damage to endothelial cells. There is also evidence that Tissue Factor is released by platelets and leukocytes. Circulating Factor VII in the blood associates with the newly exposed Tissue Factor and becomes activated (it is now called Factor VIIa). The complex of Tissue Factor and Factor VIIa (known as the Extrinsic Tenase complex) forms on the phospholipid surface of platelets. Tenase activates Factor X and Factor IX (to form Factor Xa and IXa).

Intrinsic pathway

Besides being able to recruit platelets, collagen is also important in the initiation of the intrinsic pathway. This pathway seems to be less important than the extrinsic pathway, as deficiencies of intrinsic pathway coagulation factors does not result in serious bleeding disorders. Following vessel injury, a complex of Factor XII, high molecular weight kininogen (HMWK) and prekallikrein forms on exposed collagen. Prekallikrein and Factor XII are activated to form kallikrein and Factor XIIa. Factor XIIa activates FXI (to form FXIa), which in turn activates Factor IX. Factor IXa is able to bind to Factor VIIIa, forming the Intrinsic Tenase complex. This complex converts Factor X to Factor Xa.
Pathway convergence

Factor Xa is the point of convergence of the intrinsic and extrinsic pathways. Factor Xa associates with Factor Va to form the prothrombinase complex, which processes Factor II (prothrombin) to form Factor IIa (Thrombin).

Thrombin

Thrombin is the major downstream effector of coagulation. Like other coagulation factors, it is a serine protease. Its major role is to convert fibrinogen (Factor I) into fibrin. Once formed, fibrin spontaneously polymerises to form a meshwork that enmeshes platelets, stabilising a growing thrombus. It also activates Factor XIII, which increases thrombus stability by covalently crosslinking fibrin fibres. In addition to coagulation, thrombin also able to activate platelets by proteolysing receptors on the platelet surface called Protease Activated Receptors (PARs). This synchronises coagulation with platelet activation, ensuring that platelets within a growing thrombus are activated.

Take a look here at some videos of coagulation:

http://www.youtube.com/watch?v=xNZEERMSeyM
http://www.youtube.com/watch?NR=1&feature=fvwp&v=MPGe-guZMqM
http://www.youtube.com/watch?v=iU-P5nyD8AQ&feature=relmfu

Arterial Thrombosis

Arterial Thrombosis is the formation of thrombus inside an artery (formation of a thrombus in a vein is known as venous thrombosis) which can lead to diseases such as heart attack and stroke. Arterial thrombosis and haemostasis share many of the same mechanisms. Both are initiated by the exposure of collagen. In haemostasis, the collagen is exposed upon vessel wall injury whilst in arterial thrombosis, the collagen is present in atherosclerotic plaques. These plaques can become unstable and rupture, leading to the adhesion of platelets and formation of a thrombus in the same way that haemostasis stops blood leakage from vascular tissues. Arterial thrombosis is haemostasis occurring in an inappropriate place.