Activity 2 - Platelets

Upon vessel injury, vasoconstriction inhibits blood loss from the damaged area but does not fully cut off blood flow. In order to plug the hole in the vessel, cells in the blood called **platelets** interact with exposed collagen to form a **thrombus**.

Platelets are small discoid cells that are present in the blood at high concentrations. In the normal circulation, platelets are kept in an inactive state by nitric oxide and prostacyclin which are released by healthy endothelial cells. However, damage to the endothelium activates platelets allowing them to stick to the vessel and aggregate to form a thrombus.

Platelet structure

Platelets are discoid shaped cells that are kept in shape by a plentiful actin cytoskeleton. Platelets possess a number of granules that contain bioactive molecules such as ADP, ATP, chemokines and growth factors. They also have an extensive network of pores and channels known as the **Open Canalicular system (OCS)** that is externalised upon platelet activation. The OCS acts as a reservoir for membrane and membrane proteins during platelet activation (see below).

Damage to endothelial cells not only stops nitric oxide and prostacyclin production, but also initiates release of a protein called **Von Willebrand Factor (VWF)**. Inactive VWF is also present in blood and binds to **collagen** which becomes exposed when endothelial cells are damaged. In this way, lots of VWF becomes concentrated at sites of vessel injury. In fast moving blood, VWF is able to engage platelets and hold them close to the exposed collagen. The interaction between VWF and platelets is weak, so does not last long. The platelet/VWF interaction can be visualised by coating a glass slide with VWF and perfusing blood over it (see Youtube video – link below). Platelets interact transiently with the VWF, looking as though they are rolling. A specific receptor called **GpIb/V/IX** on the surface of platelets is responsible for binding to VWF.

Click here to see a video of platelets interacting with VWF under conditions of blood flow:

http://www.youtube.com/watch?v=lWKcTmQdQ0&feature=youtu.be

Click here to learn more about haemophilia:

http://www.haemophilia.org.uk/bleeding_disorders/bleeding_disorders/von_willebrand_disease

Platelet activation

The transient interaction between VWF and GpIb/V/IX keeps platelets close to the exposed collagen for a short period of time. If enough collagen is exposed, other platelet membrane
receptors are able to bind. Binding of one receptor, known as glycoprotein VI (GpVI) to collagen generates a signal that triggers **platelet activation**. Platelet activation constitutes a number of different processes that are designed to ensure that the injury site is blocked to prevent blood loss, and to initiate mechanisms that will lead to healing of the damaged tissue. Platelet activation consists of: **shape change, integrin activation, granule release** and **phospholipid exposure**.

**Shape change**

Platelet activation results in dramatic rearrangements to the platelet’s cytoskeleton that changes the platelet from a discoid cell into a flat cell. This gives the activated platelet a large surface area, increasing the chance of plugging the injury. Extra cell membrane that contributes to the increased surface area of the platelet comes from the OCS (see above), which is externalised upon activation. This extra membrane contains a large number of membrane receptors that contribute to platelet-platelet interactions and support the formation of a thrombus.

**Integrin activation**

The major end-point of platelet activation is the activation of a membrane protein called integrin $\alpha_{IIb}\beta_3$. Upon activation, this receptor becomes able to bind the soluble protein fibrinogen with a high affinity. Different $\alpha_{IIb}\beta_3$ receptors on adjacent platelets can bind to the same fibrinogen molecules, resulting in strong adhesion of the platelets to each other. The accumulation of large numbers of platelets by this mechanism results in the formation of a thrombus.

**Granule release**

Platelets possess a number of intracellular granules that contain a number of bioactive molecules such as ADP, ATP, chemokines and growth factors which have different roles in haemostasis. ADP and ATP activate neighbouring platelets, recruiting them into a growing thrombus. Chemokines and growth factors cause the migration and growth of cells that will eventually repair the damaged vessel wall.

**Phospholipid exposure**

In resting platelets, active processes ensure that negatively charged phospholipids (phosphatidylserine and phosphatidyethanolamine) are retained in the inner side of the lipid bilayer. Upon activation, the composition of lipids is scrambled, resulting in the exposure of negatively charged lipids on the outer membrane where they can come into contact with **Coagulation Factors** (see below). Phospholipids are an essential cofactor in the initiation
of coagulation, ensuring that coagulation occurs on adhered platelets, close to the site of injury.

The outcome of platelet activation is to firmly anchor the platelet to the area of damaged vessel and to increase platelet-platelet interactions. This results in the accumulation of a group of platelets, known as a thrombus.

Further details of the molecular mechanisms regulating platelet activation can be found here: http://www.youtube.com/watch?v=mme_5Q4faXA