2.1: Pathology

The circulatory system distributes blood throughout the body, carrying oxygen, nutrients, and hormones to different organs, while removing carbon dioxide and other waste products. Blood contains multiple components including blood cells and an array of different proteins, lipids, and carbohydrates. Maintaining a constant flow of blood is essential for viability of all organs and tissues. **Venous thromboembolism** (**VTE**) refers to a blockage that occurs from a blood clot in the veins and impedes blood flow. There are generally two types of VTE, which refer to the location the blockage – deep vein thrombosis (DVT) or superficial vein thrombosis (SVT). Superficial veins are closer to the surface of the skin and are often translucently visible. Blood clots that occur in these regions usually resolve naturally (on the timescale of hours to days) and are less medically serious unless they travel to the deep veins (such as within the legs). Conversely, DVT can lead to life-threatening conditions including pulmonary embolisms and must be treated as soon as possible.

Blood Flow Blockages

Blockages that occur in the blood have different names. If blood cells aggregate and form a semi-solid mass that is attached to a blood vessel, this is referred to as a **thrombus**. If this thrombus detaches from the blood vessel, it is referred to as a **blood clot**. This is a minor but significant difference. For example, if blood is left in a test tube and coagulates into a semi-solid mass, it would be called a blood clot (and not a thrombus) because it is not attached to any blood vessels. A blood clot is also a specific example of an **embolus**, which is a substance that travels through the blood stream and can create a blockage. Blood clots, gas bubbles, cholesterol aggregates, or foreign bodies can all be identified as emboli within the blood stream.

There are situations in which blockage of blood flow is required, especially when there is damage to the circulatory system and bleeding occurs. In this case, the body has a system of responses to limit bleeding and repair the damage. This occurs in two stages called **primary hemostasis**, where platelets assemble in the area of damage and start to stick to each other, and **secondary hemostasis** (or **coagulation**), where a mesh of proteins (mostly a protein called fibrin) forms to hold the platelets together. During coagulation, the strands of fibrin protein wrap around the platelet plug that forms during primary hemostasis and become insoluble (via the action of FXIIIa), helping block the loss of blood.

Coagulation Cascade

Coagulation or the clotting of blood is controlled by “clotting factors” or “coagulation factors” in the biochemical pathway known as the coagulation cascade. In total, there are 12 clotting factors labelled with Roman numerals (I, II, III, IV, V, VII, VIII, IX, X, XI, XII, and XIII). Note that there is no clotting factor VI, since these proteins were numbered in the order of their discovery, and the protein species identified as clotting factor VI was later recognized as a different version of clotting factor V. Importantly, the clotting factors exist in two forms, an active form and an inactive form. The active form is labelled with a lower case ‘a’ following the Roman numeral. In addition to this naming convention, specific active and inactive factors have common names, which are identified in Figure 2.1.

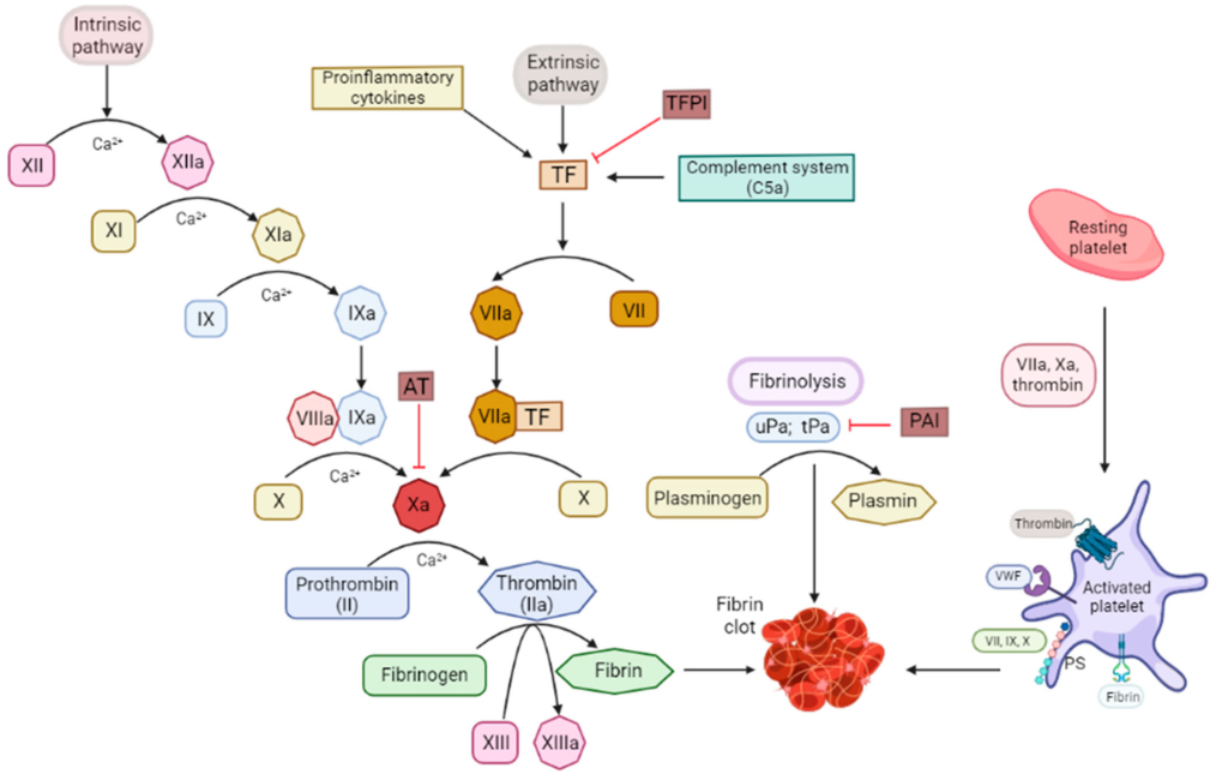

Figure 2.1 The coagulation cascade. Note that both the intrinsic and extrinsic pathways converge on activation of factor Xa. (Adapted from Guillamat-Prats, IJMS, 2022) Image source: (Figure 1) by Raquel Guillamat-Prats is used under a CC-BY 4.0 license.

These factors all participate in the coagulation cascade, which has an end-goal of creating fibrin protein (factor Ia) for the insoluble mesh formation. Several of these factors are enzymes with serine protease activity that will cleave and activate the downstream factor. The biochemical underpinnings of the full cascade are complex and can be initiated when there is internal vascular endothelium damage (intrinsic pathway) or external trauma (extrinsic pathway). Regardless, both pathways converge of activation of factor X to Xa, which leads to activation of thrombin (IIa) and fibrin (Ia). This pathway is also naturally regulated by the protein **anti-thrombin**, which can bind thrombin (IIa), but also has activity for blocking factor Xa.

The goal for anti-coagulation treatments is to interfere with any of these processes in the coagulation cascade, which will effectively enable shutting down the fibrin formation process and forms the mechanism for all anti-coagulants that are currently on the market.
