Module 5 Assignment

585.751 Immunoenginnering

1. Describe the stages of normal wound healing, including the time course and major cellular players of each stage (1-2 sentences for each stage).
   How is this process impacted by biomaterial implantation? (40 points)
   - **Inflammatory Phase:** occurs immediately and can last to 2-5 days. During hemostasis, the blood vessels constrict to stop the bleeding and platelet cells form a clot, preventing further blood loss. These clots, as they dry, turn into a scab and it is followed by an inflammation characterized by opening of the blood supply and infiltration of immune cells, particularly, macrophages, which help in cleaning the wound.
   - **Proliferative Phase:** can take 5 days to 3 weeks. The wound is rebuilt with new tissue made up of collagen. A new network of blood vessels is constructed. Myofibroblasts cause the wound to contract by pulling the wound edges together. Finally, epithelization of the wound happens when epithelial cells migrate across the granulation tissue to form a barrier between the wound and the environment.
   - **Maturation Phase:** 3 weeks to 2 years. Collagen is remodeled to strengthen the wound. However, this process often results in alterations of composition of the collagen fiber and leads to the formation of a scar which generally only have 80% of the strength of the original tissue.

   The differences with normal wound healing, is that the implantation of a biomaterial can cause foreign body response, which can lead to prolonged inflammation, especially if the biomaterial is permanent. The foreign body response is composed of foreign body giant cells which are fused macrophages that form when macrophages are unable to phagocytose the biomaterial. The foreign body reaction starts with the acute inflammatory response with presence of neutrophils and mast cells, then chronic inflammation occurs with the infiltration of monocytes and lymphocytes which can lead to the formation of granulation tissue, foreign body giant cell, and ultimately the fibrous encapsulation of the biomaterial as the result of fibroblast proliferation and capillary formation.

2. Explain frustrated phagocytosis.
   How can it still lead to biomaterial degradation by macrophages and neutrophils?
   How does macrophage frustrated phagocytosis lead to the formation of foreign body giant cells and what is their role? (30 points)

“Frustrated phagocytosis” occurs when phagocytic cells, like macrophages are unable to engulf and eliminate foreign material resulting in their fusion and the formation of foreign body giant cells (FBGCs). Even if the biomaterial is not directly engulfed by neutrophils or macrophages, it can still become coated with opsonins like antibodies and complement proteins such as C3b. Neutrophils or macrophages possess receptors for these opsonins, enabling them to bind to the material. Once bound, these immune cells can release extracellular products to try to degrade the biomaterial. FBGCs can engulf material between 1-100 um. If the material is larger, FBGCs may release their digestion products extracellularly still contributing to the degradation of the material.

3. Discuss potential mechanisms for and differences between hyperacute, acute, and chronic rejection of a transplanted organ. (30 points)

- **Hyperacute rejection** is a very rapid rejection that occurs quickly after transplantation. It is mediated by complement-dependent reactions, and it is triggered by pre-existing alloantibodies, primarily directed against blood group antigens and polymorphic MHC antigens. These antibodies bind to antigens present on the vascular endothelial cells of the graft, initiating the complement and blood clotting cascade. The vessels of the graft can become blocked leading to immediate graft failure. Hyperacute rejection is rare because donors and recipients are routinely blood type matched and cross-matched.
- **Acute rejection** occurs within several days to a few weeks, it involves endothelialitis, interstitial inflammation, injury to the graft parenchyma and blood vessels. Acute reaction is driven by alloreactive T cell and antibodies which formed once the tissue was grafted. Acute rejection triggered by activated CD8+T cells is much more common and leads to the graft parenchyma injury whereas antibody-mediated rejection is relatively rare. It can be reduced by optimizing HLA matching or mitigated with immunosuppression.
- **Chronic rejection** is the gradual deterioration of vascularized grafts. It can take months to years to develop. Chronic allograft injuries is typically irreversible, progressive and will lead to complete failure of the allograft function. Chronic allograft vasculopathy, is characterized by concentric arteriosclerosis within the graft blood vessels. The process leads to hypoperfusion of the graft and the eventual fibrosis and atrophy of the graft. This can be caused by recurrent acute rejection events, and the presence of allo-specific antibodies targeting the vascular endothelium of the graft. In liver transplant, chronic rejection is associated with bile duct loss, while in transplanted lungs, late organ failure is primarily due to bronchiolar scar tissue accumulation. Other factors to chronic graft dysfunction include ischemia, reperfusion injury, viral infections from the immunosuppression, and even the recurrence of the original disease that initially required the transplant.