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From: J. J. Russell

### The Wound Repair Process

Accidents involving insults such as physical trauma can induce several types of wounds i.e. incisions, punctures, burns, lacerations and abrasions. Incisions are cuts caused by broken glass and other sharp objects. Objects like pins, nails, and metal/ wood splinters, piercing the skin layers and leaving a depression or hole cause punctures. Burns from hot metal, hot liquids, chemicals or fire can cause damage to the various skin layers. Lacerations are irregular jagged cuts or tears of the skin layers that usually also produces some amount of bleeding. Abrasions are caused by scraping of the outer layers of the skins surface against the rough surface of another object and are often accompanied by foreign material being embedded in the wound site. Other physical features of a given wound such as size of area, depth, severed blood vessels and cell or tissue type, help govern the type and length of the wound repair process. Normal adaptive physiological processes in response to such events include increased cellular activity, decreased cellular activity and change or alteration in cell type.

The general wound repair process is a multi-step series of overlapping events and is illustrated schematically in Table 1. However, this schema is not meant to represent all of the known myriad events involved in the wound repair process. Moments after the wound has occurred, disruption and destruction of local tissue morphology and histology and blood vessels initiates a cascade of events that lead ultimately to repair of the injury site. The first phase of wound repair, generally referred to as inflammation, results from the release of blood cell components, i.e. chemokines and coagulation factor VIII that attract numerous cells to the wound site. Platelets, guided by coagulation factor VIII (also known as von Willebrand's factor) arrive at the wound site first to stop the bleeding. Arriving next are usually neutrophils to remove contaminating bacteria. Monocytes are next to arrive and they transform into macrophages that phagocytize dead and dying cells and cellular and tissue debris. This inflammation period, often referred to as early and late inflammation, can last up to 10 days following the wound-induced broken blood vessel event. The infiltrating macrophages also produce a variety of cytokines and growth factors, including transforming growth factor (TGF- $\beta$ ), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF- $\alpha$ ) and platelet-derived growth factor (PDGF). These factors not only induce the recruitment of cells to the wound site but also are necessary for the induction of the granulation tissue phase beginning approximately on day two after the initial wound and continuing for about three weeks. Growth factors are pleiotropic extracellular signaling proteins and peptides that exhibit a variety of biological events including modulating cellular reactions following perturbation i.e. wounds. The granulation phase is characterized by an increasing number of macrophages, proliferation of fibroblasts, extracellular matrix (ECM) or loose connective

tissue development and angiogenesis or newly formed blood vessels. The maturation phase, which begins within days after wounding and can last for several months, is characterized by a decreasing number of macrophages as a prelude to maturation of the ECM including collagenous scar tissue formation and a repopulation of the local wound site cell / tissue types. Clinical studies have shown that a consistently elevated number of macrophages at a wound site are associated with a delay in wound healing (Choi et al. *Plas. Reconst. Surg.* 96:1177-1185 (1995)).

TGF- $\beta$  functions both as an inhibitory and stimulatory factor and when released at a wound site by platelet degranulation induces other effector cells, protein matrix synthesis and angiogenesis and fibrosis associated with wound healing (Roberts and Sporn in *Human Cytokines*, Blackwell Scientific, p 399 (1992)). Conversely, overproduction of TGF- $\beta$  or other growth factors are involved in progression of putative precancerous cells to malignancy and pathogenic fibrosis (Sieweke et al. *Science*, 248:1656-1660 (1990)). Il-1 is produced by a number of cell types including macrophages, monocytes, fibroblasts and epithelial cells. Some Il-1 bioactivities include enhanced synthesis of PDGF by fibroblasts, increased collagen production, modulation of tissue repair following injury, fibroblast activation and accelerated wound healing and angiogenesis (Quarnstrom et al. *J. Biol. Chem.* 263:8261 (1988)). Il-6 also exhibits multiple bioactivities including weak antiviral activity, induces cellular proliferation in some cell types and growth inhibition in others. PDGF was first identified by Ross et al. while studying wound healing and atherogenesis (Ross et al. *Science*, 180:1332 (1973)). PDGF bioactivities include growth and proliferation of a variety of cell types, induces chemotaxis, stimulates vasoconstriction, enhances erythropoiesis, and stimulates wound healing (Seppa et al. *J. Cell Biol.* , 92:584 (1982), Berk et al. *Science*, 232:87 (1986)).

A general description of the normal wound repair process is described above. However, the exact nature or perhaps synergy of the physiological response that occurs when an acute wound produced by a cut, puncture, abrasion etc is accompanied by hot acidic or corrosive solutions that may or may not contain radioactive materials i.e. Pu, Am or U is largely unknown. It is known however that cell sensitivity to radiation varies extensively throughout the cell cycle. As a consequence, cells alter their transit through the cell cycle after exposure to radiation. Such exposed cells may delay in G1, S, G2 or mitosis and thus affect the normal wound healing process. Consequently, chronic irradiation from extravasated deposits of thorium dioxide has induced delayed wound healing at the site of Thorotrast injections in some patients. However, how the resulting dose and or dose rate from embedded particles of actinide materials affect the overall multi-step wound repair process remains poorly understood.

## References

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Table 1.

A general description of the wound repair process.

