

Stimulating Biological Mechanisms of Body Repair: From Wound Healing to Anti-Aging Regenerative Rejuvenation

Healing is the interaction of a complex cascade of cellular haemostasis, inflammation, proliferation and migration, followed by scar tissue remodeling. All these events are based on the same cell communications that transcend aging.

Healing is much slower with age due to aberrant cell communications leaving the body with inappropriate levels of Growth factors and connexins resulting in hypo or hyperproliferation or sustained inflammation. Unbalanced levels of hormones, insufficient oxygen and cell sustaining nutrients are additional determining factors of healing and aging .

Diabetic ulcers are associated with reduced supply of oxygen and other nutrients, prolonged inflammation, impaired neovascularization, decreased synthesis of collagen, increased level of proteinases and defective macrophage function. Keloids involve increased activity of fibrogenic cytokines such as TGF b1, IGF01 and interleukin-1 and mutations in regulatory genes such as p53. The same unbalanced processes are observed in aging. Keratinocytes, fibroblasts and vascular endothelial cells display a reduced proliferative response in the aged. Re-epithelization and collagen synthesis exhibit a delay. There is a general decrease in the number and size of dermal fibroblasts and aged fibroblasts exhibit a diminished response to growth factors

Fetal wounds re-epithelialize rapidly due to the small amount of TGF b1 in fetal skin. Scarring has been reduced in experimental studies that suppress TGF b1 and b2 by utilizing TGF b3 that downregulates the other TGF growth factors

Research in wound healing demonstrate that keratinocytes adopt a migratory phenotype as they start to crawl across the wound bed to close the epidermal breach. Wound healing brings together cells from distant positions and involves processes such as DNA synthesis and cell proliferation. Growth Factors Signaling is necessary for cell movement into wounds. Transforming growth factors (TGF) b1, b2, transforming factor a, Fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factors (PDGF) AB and BB, insulin growth factor (IGF-1) and Keratinocyte Growth Factor (KGF) TGF b1, FGF and PDGF are proinflammatory agents and have proven successful in promoting different aspects of wound healing such as cell proliferation and migration. Proteinases signaling are necessary for cell movement into wounds, urokinase-type plasminogen activator (uPA), matrix metalloproteinases (MMPs) such as collagenase 1, gelatinase A, collagenase 3, and tissue plasminogen activator (t-A)

Connexins are also crucial in wound healing. Cx43 increases in blood vessels in and around the site of injury. Downregulation of Cx43 by Antisense has the effect of speeding the migration of keratinocytes and fibroblasts which results in closing the wound and forming the granulation tissue considerably faster. It also results in

reducing negative effects such as inflammation. Cx26 has been associated with hyperproliferative conditions delaying remodeling and recovery. Clearly the appropriate levels of connexin expression are crucial for normal healing to take place.

Research is now focused on collagen receptors and signaling pathways in relationship to wound healing. Collagen receptors such as DDR1 are not essential for wound healing. However, the collagen receptor DDR2 is crucial for wound healing. Statistical Analysis using the Fisher exact test showed that there was a mild but significant difference ($p < 0.05$) between controls and experimental subjects whereas up-regulating the JNK (c-Jun NH₂-terminal kinases) signaling pathway increases wound healing and down-regulating the JNK signaling pathway slows down wound healing. Recent research (Suh 2002) demonstrated that aging is associated with a molecular signaling defect in the JNK pathway that impairs the balance between cell survival and apoptosis. While increased apoptosis could lead to cell loss, loss of apoptosis competence results in the an increase of cancer incidence. Again, the key is a balance between apoptosis and cell survival. Researchers such as Wang et al (2003) introduce the JNK signaling pathway as a genetic determinant of aging. They demonstrate that the JNK functions at the center of a signal transduction network that coordinates the induction of protective genes in response to oxidative challenge. JNK signaling activity thus alleviates the toxic effects of reactive oxygen species (ROS)

In conclusion, any aberrant communication between cells and their surrounding ECM delay or obstruct wound healing. Aberrant communications between cells and their surrounding ECM also leads to aging. A number of studies examining protein to protein interactions in aged and young subjects demonstrated that Aging is the result of disorganized protein to protein interactions