CIRCADIAN SKIN IS A REALITY :

The secrets of skin repair in body tuning, wound healing and anti-aging

Historically, work on peripheral circadian clocks has been focused on organs and tissues that have prominent metabolic functions, such as the liver, fat, and muscle. In recent years, skin has emerged as a model for studying circadian clock regulation of cell proliferation, stem cell functions, tissue regeneration, aging, etc. Morphologically, skin is complex, containing multiple cell types and structures, and there is evidence for a functional circadian clock in most, if not all, of its cell types. Despite the complexity, skin stem cell populations are well defined, experimentally tractable, and exhibit prominent daily cell proliferation cycles. Healing is the interaction of a complex cascade of cellular hemostasis, inflammation, proliferation and migration, followed by scar tissue remodeling. All these events are based on the same cell communications that trascend aging. Due to the accessibility of skin, in vivo imaging techniques can be readily applied to study the circadian clock and its outputs in real time, even at the singlew cell level. Skin provides the first line of defense against many environmental and stress factors that exhibit dramatic diurnal variations such as solar ultraviolet (UV) radiation and temperature. Studies have already linked the circadian clock to the control of UVBw induced DNA damage and skin cancers. Due to the important role that skin plays in the defense against microorganisms, it also represents a promising model system to further explore the role of the clock in the regulation of the body's immune functions. To that end, recent studies have already linked the circadian clock to psoriasis, one of the most common immunew mediated skin disorders. Hand in hand with skin circadian clocks is the extensive signalling within and between cells. We believe that the two are linked and work together. In the signaling arena, we observe that 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 hormonal signal, RBC's aggregation leading to insufficient oxygen and cell's inability to sustain nutrients are additional determining factors of wounds 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. Keratonicytes, fibroblasts and vascular endothelial cells display a reduced proliferative response in the aged as a result of reduced signaling. Re-epithelization and collagen synthesis exhibit a delay again due to deficient signaling. There is a general decrease in the number and size of dermal fibroblasts. Aged fibroblasts exhibit a diminished response to growth factors, in other words, their aging process is related to diminished hormonal signaling.

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 an event that is interrelated with activities in specific signaling pathways. Again via signaling mechanisms, 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 be, transforming factor a, Fibroblast growth factors (FGF), vascular endothelial growth factos 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 a cell proliferation and migration. Proteinases signaling are necessary for cell movement into wounds, urokinase-type plasminogen activator (uPA), matrix matelloproteinases (MMPs) such as collagenase 1, gelatinase A, collagenase 3, and tissue plasminogen activator (t-A)
Connexins are also crucial in wound healing. C 43 increases in blood vessels in and around the site of injury. Downregulation of Cx43 by Antisense has the effect of speeding the migration or 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. Clinically, we have tried to enhance signaling related to wound healing by a device that combines circadian timings with signaling specifications known to enhance fibroblast secretion, collagenase 1 and 3, Keratinocyte growth factors and certain pro-inflammatory agents. Results of single study studies have been encouraging as shown by the before and after pictures provided

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, we propose a combination of signaling and timing as an aspect of circadian rhythms as well as circadian clocks to be instrumental in wound healing as well as the aging process. 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 or desease. 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. Correct timing and meaningful signals sent and received by cells during their whole existence are essential for the harmonious development, maintenance and survival of tissues, organs and bodies. Timing and Signaling also govern movement, thought and behavior of cellular «microsocieties» whose proper functioning requires a precise coordination of emission and reception of signals. This perspective combines timing, circadian rhythms and signalling communications in an organized complex that could serve as the cornerstone of Anti-aging, Regenerative and Preventive Medicine