**Sirtuins in wound healing**

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**ABSTRACT**

Sirtuins (SIRTs) are initially recognized as NAD\(^+\)-dependent histone deacetylase. SIRTs attract attention for their role as calorie restriction-induced “longevity proteins” to be expected to extend human life span and to promote health. As advancing studies, SIRTs have been recognized as cell signaling regulators which contribute to anti-inflammation, cell differentiation and so on. Therefore, SIRTs are supposed to affect wound healing which is comprised highly orchestrated complex four phases: hemostasis, inflammation, tissue formation and tissue remodeling. This review highlights the roles of SIRTs in wound healing process and provides a foundation and impetus for future basic and clinical research.

**Keywords**: sirtuin; wound healing; anti-inflammation; re-epithelialization

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**Introduction**

Since the discovery of silent information regulator 2 (SIR2) gene in 1997, SIRT, the SIR2-like genes, have been found in bacteria, plants and animals, and their function has been investigated the key roles. Sir2 protein was initially identified as a member of NAD\(^-\)-dependent deacetylases and ADP-ribosyltransferases in *Saccharomyces cerevisiae*\(^1\) and subsequent studies showed that SIR2 extends replicate life span of yeast by suppressing rDNA recombination and decreasing extrachromosomal rDNA circle\(^2,3\). Following the studies on longevity of life span in *Caenorhabditis elegans* and *Drosophila*\(^4-6\), the studies on mammalian sirtuins embarked. Human sirtuins comprise seven members of protein (SIRT1–7) localized in cytosol, nucleus and mitochondria, which are involved in pleiotropic cellular functions by deacetylation of histone and/or non-histone proteins (Table 1). The SIRTs attract attention for their role as calorie restriction-induced “longevity proteins” to be expected to extend human life span and to promote health\(^7-9\). The primary function of skin, dominantly comprised by fibroblasts and keratinocytes, is to serve as a protective barrier against environment. Wound, which disrupts the primary function of skin, may lead to major disability or even death. Chronic skin ulcers such as bedsore and diabetic foot ulcer emerged as the issue to be addressed in “aged society”, as well as acute wounds caused by injury and burns in all generations. On the other hand, previous studies suggested that SIRTs expressed in fibroblast and keratinocyte may concern cutaneous physiology. However, their role is gaining interest in the field of dermatology. Herein this review highlights the role of SIRTs in wound healing.

**Acute Wounds**

Wound healing is a physiological response to restore skin integrity and is comprised highly orchestrated complex four phases: hemostasis, inflammation, tissue formation and tissue remodeling\(^10\). In inflammation phase to begin with the formation of a hemostatic plug by aggregated platelets, many kinds of mediators are involved through the wound healing processes. Previously, a great deal of studies focused on growth factors, cytokines and chemokines in the process (Table 2)\(^11\). Platelets aggregated around the wound site not only...
facilitate the formation of a hemostatic plug, but also secrete kinds of mediators such as platelet-derived growth factor (PDGF), that attracts and activates macrophages and fibroblasts. The activation of infiltrated cells and residing cells in wound site leads to up-regulation of proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α in inflammation phase. IL-1 released from macrophages and keratinocytes induces keratinocyte migration for re-epithelialization and the secretion of FGF-7 from activated fibroblasts for extracellular matrix formation\[^{[28,29]}\]. IL-6 expression is induced in neutrophils and macrophages immediately after wounding and the expression is sustained during healing process\[^{[18,19]}\]. IL-6 attracts neutrophils which cleanse the wound site of foreign particles and bacteria. Additionally, IL-6 has a mitogenic and proliferative effect on keratinocytes for re-epithelialization\[^{[22,23]}\]. A previous study suggested that TNF-α accelerates re-epithelialization \textit{via} induction of FGF-7 in fibroblasts like IL-1\[^{[31]}\]. However, TNF-α has also been reported to suppress the wound healing \textit{via} the induction of type V collagenase at the high concentration\[^{[22]}\].

Nuclear factor kappa B (NF-κB), a transcription factor, is well-known as a major regulator of proinflammatory cytokine expression. In unstimulated cells, NF-κB is bound to inhibitory protein, IκB, localizing in cytosol. Extracellular stimuli recognized by receptors initiates a signaling cascade leading to the activation of IκB kinase (IKK). The phosphorylation of IκB by IKK induces degradation of IκB by proteosome and releases NF-κB from the complex. The freed NF-κB translocates into the nucleus where it binds to the target gene promoter region and activates gene transcription\[^{[33]}\]. Yeung \textit{et al.} demonstrated that SIRT1 inhibits the transcriptional activity of NF-κB by deacetylation of RelA/p65 subunit of NF-κB\[^{[34]}\]. Indeed, resveratrol (RSV), a well-known SIRT activator, inhibited IL-6 production from normal human dermal fibroblasts by lipopolysaccharide, which binds to TLR4 and activates NF-κB, in our laboratory (Figure 1). TNF-α, which is a pivotal cytokine in inflammation, up-regulates the expression of matrix metalloproteinase-9 (MMP-9), IL-1β and IL-6 in 3T3 fibroblasts. SIRT1 activation by RSV suppressed TNF-α expression by the inactivation of NF-κB, followed by down-regulation of MMP-9, IL1β and IL-6\[^{[35]}\].

Other than peptide mediators, nitric oxide (NO), a short-lived free radical, has been reported as a regulator in wound healing. NO is formed from arginine by NO synthase (NOS) which exist in three distinct isoforms, two constitutive (endothelial and neuronal) isoforms and one inducible isoform. The highest NOS activity was detected in the early phase in wound healing\[^{[36]}\] followed by sustained NO synthesis\[^{[37]}\] and the highest expression of inducible NOS was confirmed in the early phase as well\[^{[38,39]}\]. During the healing process, NO is involved in re-epithelialization, neovascularization and collagen synthesis\[^{[40]}\]. SIRT1 activation suppressed inducible NOS (iNOS) expression through the inhibition of

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**Table 1. Sirtuins**

<table>
<thead>
<tr>
<th>Sirtuin</th>
<th>HDAC Class</th>
<th>Localization</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirtuin 1</td>
<td>Class I</td>
<td>Nucleus/Cytosol</td>
<td>Cell survival/Life span regulation/Metabolism regulation/Inflammation/Oxidative stress response</td>
</tr>
<tr>
<td>Sirtuin 2</td>
<td>Class I</td>
<td>Nucleus/Cytosol</td>
<td>Cell cycle regulation/Nerve system development</td>
</tr>
<tr>
<td>Sirtuin 3</td>
<td>Class I</td>
<td>Nucleus/Cytosol</td>
<td>Mitochondrial metabolism</td>
</tr>
<tr>
<td>Sirtuin 4</td>
<td>Class II</td>
<td>Mitochondria</td>
<td>Mitochondrial metabolism</td>
</tr>
<tr>
<td>Sirtuin 5</td>
<td>Class III</td>
<td>Mitochondria</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>Sirtuin 6</td>
<td>Class IV</td>
<td>Nucleus</td>
<td>Genome stability/DNA repair</td>
</tr>
<tr>
<td>Sirtuin 7</td>
<td>Class IV</td>
<td>Nucleus</td>
<td>rRNA transcription regulation/Cell cycle regulation</td>
</tr>
</tbody>
</table>
TNF-α expression, SIRT1/2 has been described to enhance endothelial NOS (eNOS) activity eliciting significant increase in NO production by deacylation at lysines 496 and 508 in the calmodulin-binding domain of eNOS. On the other hand, class I histone deacetylase (HDAC2), which is the only member of this class known to be S-nitrosylated directly by NO inhibits the expression of growth factors such as epidermal growth factor (EGF) by attaching the promoter regions. These suggest that post-translational S-nitrosylation of HDAC2 leads to enhance the production of growth factors by detachment of HDAC2 from the promoter regions. Consequently, SIRT-dependent NO production enhances wound closure by evocation of keratinocyte proliferation. Taken together, SIRT1 engages profoundly with the expression of proinflammatory mediators, suggesting SIRT1 could be one of the therapeutic targets for wound healing.

**Table 2. Growth factors and cytokines in wound healing**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Source</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platele-derived growth factor</td>
<td>Platelet, Macrophage, Keratinocyte</td>
<td>Fibroblast proliferation, Chemoattraction</td>
</tr>
<tr>
<td>Vascular endothelial growth factor</td>
<td>Epidermal cell, Macrophage</td>
<td>Angiogenesis, Increase vascular permeability</td>
</tr>
<tr>
<td>Epidermal cell growth factor</td>
<td>Platelet, Macrophage, Fibroblast</td>
<td>Cell migration, Cell proliferation</td>
</tr>
<tr>
<td>Fibroblast growth factor</td>
<td>Macrophage, Mast cell, Endothelial cells, Keratinocyte, Fibroblast</td>
<td>Angiogenesis, Fibroblast proliferation, Keratinocyte migration</td>
</tr>
<tr>
<td>Transforming growth factor b1</td>
<td>Platelet, Macrophage, Lymphocyte, Keratinocyte, Fibroblast</td>
<td>Cell migration, Chemoattraction, Granulation tissue formation, Re-epithelialization, Extracellular matrix synthesis</td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>Neutrophil, Macrophage</td>
<td>Growth factor expression, Re-epithelialization</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>Neutrophil, Macrophage, Fibroblast</td>
<td>Initiation of inflammation, Re-epithelialization</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Neutrophil, Macrophage, Fibroblast</td>
<td>Re-epithelialization, Formation of granulation tissue, Angiogenesis</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>Neutrophil, Macrophage</td>
<td>Re-epithelialization</td>
</tr>
</tbody>
</table>

**Chronic Wounds**

Chronic wounds are defined as those which do not follow the normal healing process and show no signs of effective healing within 3 months after the injury. The cause of failure to complete wound healing is mainly to stagnate at the early inflammation phase. The features characteristic for the chronic wounds are shown in Table 3. Avishai et al. demonstrated risk factors such as autoimmune diseases, aging, obese and diabetes mellitus. In “aged-society”, the strategy of therapy for chronic wounds is the issue to be addressed, because older adults suffering from vascular disease, venous insufficiency, unrelieved pressure and diabetes mellitus, are more likely to have chronic wounds than younger people. As the morphology of resident cells is similar to that seen in senescent cells in chronic wounds, it is supposed that the treatment against cell senescence as well as against prolonged inflammation. Expression of aging...
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Biomarkers including procollagen I and VII, SIRT1 and SIRT6 were down-regulated in passaged human dermal fibroblasts \[51\]. Growth of chronic wound fibroblasts was significantly decreased compared with fibroblasts isolated from acute wound and normal dermis \[52\].

By SRT2127, a small molecular SIRT1 activator \[54\]. In skin, RSV and metformin significantly inhibited up-regulation of MMP-9 expression and prevented collagen degradation after ultra-violet irradiation \[55\]. Similarly, SIRT6 has been reported to regulate negatively the expression of MMP-9 \[56,57\]. It is easily presumed that this negative regulation of MMP-9 expression is due to inhibition of NF-κB pathway, because MMP-9 expression is regulated by NF-κB which is a deacetylation target of SIRTs. Like so, suppressed MMP-9 expression contributes to collagen re-modeling in dermis. However, MMP-9 deficiency leads to impaired wound healing, because MMP-9 also contributes keratinocyte migration in re-epithelialization phase. On the other hand, high glucose impaired keratinocyte migration by inducing levels of MMP-9 expression in diabetic mouse model. This glucose-sensitive elevation of MMP-9 expression was blocked by deletion of FOXO1, which is also a deacetylation target of SIRT1, concomitant with improved wound healing \[58\]. Therefore, the appropriate expression of MMP-9 is required for orchestrated wound healing process.

Conclusion

SIRTs attract attention for their role as calorie restriction-induced “longevity proteins” with expectation to extend human life span by promoting health and wellness. As studies advance on SIRTs, it has been emerged that SIRTs are involved in pleiotropic functions via deacetylation of histone and/or non-histone proteins (Figure 2) \[59\]. Of them, inflammation, cell proliferation and cell migration are vital events in wound healing process. SIRTs have not only anti-inflammatory effects but also promotive effect on cell proliferation and cell migration to enhance wound healing, suggesting SIRTs activation could be one of the therapeutic strategies for wound healing. SIRTs activators have been found in nature and synthesized such as RSV and its derivatives \[60\]. The effect of RSV on wound healing and chronic diseases has been evaluated not only in animal model and human EpiDerm full thickness model, but also in clinical applications \[61–63\]. Taken together, SIRTs are involved in orchestrated wound healing processes and its activation provides an approach for acceleration of wound therapy. RSV could be a major candidate compound for wound healing because it is a polyphenol found in nature such as within plants, or the consumed such as grapes and wine.
**Conflict of interest**

The author declares no potential conflict of interest with respect to the research, authorship, and/or publication of his article.

**References**


