We consider that from the wound to the healing process, the physiology point key to linkage of the process is still unclear. The process from inflammation to the wound healing is divided into three phases: (1) inflammation process, (2) tissue formation, and (3) tissue remodeling. The inflammation program includes cell produced related factors and immune cells infiltration. We thought the inflammation factors that may be also involved in the followed healing process. But the question is “what kind of factor is the major key involved in the end of the inflammation then to initiate the healing.” We suspect that the apoptosis of immune cell may be the major key to end of inflammation and to initiate the healing.

Keywords: apoptosis, inflammation, wound healing, cellular physiology, wound repair

INFLAMMATION PROCESS
Inflammation is known to be a crucial adaptive response for animals, and the mechanism is a complex interaction with molecular mediators even the functions of immune cells in a microenvironment through a response that occurs at all levels of biological organization (Allavena et al., 2008). In this process, cooperation among cells and mediators occurs, and a wide range of factors are involved in the classical immune response, including the stage of the inflammation process; the tissue or organ involved, and whether the inflammation is acute and resolving or chronic and non-resolving (Punchard et al., 2004). The inflammation process involves vascular permeability, active migration of blood cells, and the passage of plasma constituents into injurious tissue (Maslinska and Gajewski, 1998). Through the infiltration of immune cells, studies have shown that the inflammation process plays a crucial role in atherosclerosis (Sharsi et al., 2007). Blood leukocytes, mediators of host defenses and inflammation, localize in the earliest lesions of atherosclerosis in experimental animals. The study of inflammation in atherosclerosis has afforded considerable new insight into the mechanisms underlying the recruitment of leukocytes (Libby et al., 2002). Recently, studies have indicated the role of inflammation in Alzheimer’s disease (AD; Schott and Revesz, 2013). Inflammatory components related to AD...
Inflammation and repair are tightly regulated and dynamic processes involving blood clotting, inflammation, formation of new tissue, and tissue remodeling. The growth factors likely to be involved are PDGF, TNF-α, and TNF-β, HGF, TGF-β2, epidermal growth factor (EGF), and fibroblast growth factor (FGF). Cytokines such as IL-1, IL-6, IL-8, IL-10, and interferon gamma (INF-γ) are also thought to play a role (Moroscacli et al., 2013). It is clearly a balance between appropriate fibroblast activation and the fibrosis that results from their continuing activation. Multiple growth factors have been implicated in fibroblast migration and activation, but much attention has been recently focused on the PDGF family of growth factors and their cognate receptors (PDGFRs; Nemenoff, 2012). Research has documented that PDGF exerts autocrine, mitogenic effects on keratinocytes to support epidermal proliferation and stabilization of the dermoeidermal junction during wound closure. In addition, it stimulates vessel maturation by recruitment and differentiation of pericytes to the immature-endothelial channels (Hellberg et al., 2010).

Studies have investigated the cytokines involved in the inflammation response by using various animal models. The expression of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), is significantly increased in the adipocytes of obese animals (ob/ob mouse, db/db mouse, and fara Zucker rat; Hotamisligil et al., 1993). The activation of TNF-α might induce leukocytes express adhesion molecules on the cell surface (Dunne et al., 2001; Bruderer et al., 2013; Li et al., 2013), leading to diabetic pedesis through individual vascular endothelial cells (Carman and Springer, 2004). IL-6 is an adipokine (Fried et al., 1998) thought to be a mediator of inflammation (Xing et al., 1998; Deng et al., 2012; Tang et al., 2012) that is produced by adipose tissue and liver-resident macrophages that are activated in response to hepatocyte death (Sakurai et al., 2008). IL-6-deficient mice exhibit a marked decrease in inflammatory response, granulation tissue formation, and re-epithelialization (Gallicchio et al., 2000). The IL-1 family, which includes IL-1α and IL-1β, exhibits strong pro-inflammatory activities and plays a major role in host responses to exogenous and endogenous noxious stimuli (Gabay et al., 2010). IL-1 induces the expression of adhesion molecules on endothelial cells and elicits stromal cells to release chemokines that promote the recruitment of inflammatory cells at the inflammation site (Dinarello, 1996; Chang et al., 2012; Wu et al., 2012). Such inflammation occurs significantly in cases of comorbidity and might contribute to the increased risk of developing cardiovascular accidents observed in these patients (Carugniano et al., 2010). IL-10, a cytokine with anti-inflammatory properties, plays a central role in infection that involves limiting the immune response to pathogens and thereby preventing damage to the host (Saraiva and O’Garra, 2010).

Recently, research has shown that IL-10 and related cytokines can facilitate the tissue-healing process in injuries caused by infection or inflammation (Qiu et al., 2011). According to these studies, mediators thought to be involved in the regulation of inflammation responses such as leukocyte recruitment, adhesion molecule expression, and wound healing in the late phase of inflammation.
IMMUNE CELL-WOUND HEALING

Immune cells are involved in virtually every aspect of the wound repair process, from the initial stages where they participate in hemostasis and work to prevent infection to later stages where they drive scar formation (Wilgus, 2008). Evidence supporting a central role for T lymphocytes in the control of wound healing is provided by studies which examine the in vivo effects of alternate forms of T cell manipulation on various parameters of healing (Barbul and Regan, 1990) and Neutrophils as important to wound healing as they help control infection, however, they also release harmful enzymes which damage healthy tissue surrounding the wound site (Brubaker et al., 2011). Investigations have enumerated many of the specific proteins that are produced by wound macrophages at the site of injury. These include the following: (1) chemotactic agents that recruit and activate additional macrophages at the site of injury, (2) growth factors that promote cellular proliferation and protein synthesis, (3) proteases and extracellular matrix molecules, and (4) factors that may restrain tissue growth once repair is completed (DiPietro, 1995). Neutrophils arrive first within a few minutes, followed by monocytes and lymphocytes. They produce a wide variety of proteinases and reactive oxygen species as a defense against contaminating microorganisms, and they are involved in the phagocytosis of cell debris. Neutrophil play a role as primarily phagocytosis appearing approximately 24 h after injury and contribute to decreasing the infection in the wound. Neutrophils are not paramount to the process of wound healing or collagen synthesis (Park and Barbul, 2004). Research has been shown a role of neutrophil in wound healing for the production of neutrophil growth factors, such as granulocyte/macrophage colony-stimulating factor (GM-CSF; Canturk et al., 2001). Experiments with cultures of keratinocytes established from —/— and +/+/ mice revealed a retardation in wound closure in CCR2 —/— keratinocytes, role for this receptor on keratinocytes in epithelial resurfacing that is independent of neutrophil recruitment (Devalaraja et al., 2000). In the resolution and regeneration stages, macrophages appear to remove large cell debris as well as apop- tootic neutrophils, the key scavengers for resolving inflammation and facilitating tissue regrowth, furthermore, experiment illustrated that the depletion of macrophages in zebrafish model leads to the delay of the clearance of cell debris, decrease of regeneration speed, and formation of vacuoles in the regenerating fin (Li et al., 2012). Recently, research has shown that wound healing requires a coordinated interplay among cells, growth factors, and extracellular matrix proteins. Central to this process is the endogenous mesenchymal stem cell (MSC), which coordinates the repair response by recruiting other host cells and secreting growth factors and matrix proteins. MSCs are self-renewing mul- tipotent stem cells that can differentiate into various lineages of mesenchymal origin such as bone, cartilage, tendon, and fat (Maxson et al., 2012).

When tissues are damaged, inflammatory mediators are released. Where macrophages and become activated by various cytokines, such as interleukin-1 (IL-1), that are released from neighboring inflammatory cells, including neutrophils, natural killer (NK) cells, resident tissue macrophages, and T cells. In the end of the inflammation, we can observe the apoptosis of the immune cells and the apoptotic cells cleared by macrophages. We thought that clearance by macrophages of cells apoptosis is a key process.
APOPTOTIC CELL-WOUND HEALING

Evidence illustrates that apoptosis is involved in the resolution of various phases of tissue repair. In the early phases of tissue repair, inflammatory cells underwent apoptosis starting as early as 12 h after wound injury (Brown et al., 1997). Examined apoptotic patterns in cells in open wounds created in rats, found that apoptosis marked observed in the inflammatory cells of the scab. In this research found that apoptosis in myofibrolasts initiated on day 12, peaked at day 20, and resolved at day 60. These findings suggest that myofibroblast apoptosis initiated about the same time at the end of the wound healing following to the healing (Desmouliere et al., 1995). Stromal keratocyte apoptosis has been well-characterized as an early initiating event of the corneal wound healing response, triggering subsequent cellular processes that include bone marrow-derived cell infiltration, proliferation, and migration of residual keratocyte cells, and, in some circumstances, generation of myofibroblasts cells (Wilson et al., 2007). Impaired phagocytosis of apoptotic neutrophils by Vav3-/- (guanine-nucleotide exchange factor implicated in leukocyte functions by relaying signals from immune response receptors and integrins to Rho-GTPases) macrophages was causal for their reduced release of active TGF-β1, for decreased myofibroblasts differentiation and myofibroblast-driven wound contraction to cause the situation of delayed wound healing (Sindiriari et al., 2009). Apoptotic cells released growth signals that stimulated the proliferation of progenitor or stem cells by caspase 3 and 7 proteases which involves the caspase-mediated activation of phospholipase A2 and the subsequent production and release of the lipid signal prostaglandin E2, a stimulator of cell proliferation and mice lacking either of these caspases were deficient in skin wound healing (Li et al., 2010). The inflammation factors that may be also involved in the followed healing process. But the question is “what kind of factor is the major key involved in the end of the inflammation then to initiate the healing.” We suspect that the apoptosis of immune cell may be the major key to end of inflammation and to initiate the healing as shown in Figure 2.

CONCLUSION

We hypothesized that the key point to end of the inflammation is the apoptotic activity of immune cells. Apoptosis is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development, and chemical-induced cell death (Elmore, 2007). In the inflammation response, the mediators induce the infiltration of activated immune cells into inflammation site to protect the tissue against the pathogen infection. In the end of the inflammation, we can observe the apoptosis of the immune cells and the apoptotic cells cleared by macrophages. We thought that clearance by macrophages of cells apoptosis is a key point phenomenon associated with actively tissue formation from wound inflammation.

REFERENCES

Agarwal, B. R., Shahoulid, S., Sandor, S. K., Pandey, M. K., and Subb, G. (2006). Inflammation and cancer: how hot is the link? Explo Blood Pharmacol. 32, 1553–1621. doi: 10.1016/j.empo.2006.06.019

Alkemade, P., Sica, A., Solinas, G., Porta, C., and Mantovani, A. (2008). The inflammatory microenvironment in tumor progression: the role of tumor-associated macrophages. Crit. Rev. Oncol. Hematol. 66, 1–9. doi: 10.1016/j.critrevonc.2007.07.004

Braud, P. (2015). Wound healing and the role of fibroblasts. J. Wound Care 22, 407–412.

Barbul, A., and Begum, M. G. (1995). The regulatory role of lymphocytes in wound healing. J. Trauma-Injury Infect. 36, 507–510. doi: 10.1097/00005373-199502001-00021

Brown, D. L., Kao, W. W. Y., and Greenhalgh, D. G. (1997). Apoptosis-regulates inflammation under the advancing epithelial wound edge: Delayed patterns in diabetes and improvement with topical growth factors. Surgery 123, 372–380. doi: 10.1016/S0039-6060(97)80358-8

Budde, A., L. Schneider, D. F., and Kovacs, E. I. (2011). Neutrophils and natural killer T cells in negative regulators of wound healing. Expert. Rev. Dermatol. 6, 5–8. doi: 10.1586/erd.10.66

Buckow, M., Alum, M., and Worlein, M. J. (2015). Role of HIF1α and VEGER in endothelial biology. J. Vasc. Res. 50, 265–278. doi: 10.1007/10535-015-0267-7

Butler, S., Berry, R., Ingham, E., and Southgate, J. (2012). The resolution of inflammation during the regeneration of biological scaffolds by human tissue. J. Tissue Eng. Regen. Med. 6, 218–218.

Cantra, N. Z., Epron, N., Vidal, B., Cantra, Z., Kiechl, G., Okere, G., et al. (2011). The relationship between neutrophilic and incisional wound healing. Skin Pharmacol. Appl. Physiol. 14, 108–116. doi: 10.1159/000049340

Carman, C. V., and Springer, T. A. (2004). A transmigratory cap in leukocyte diapedesis both through individual vascular endothelial cells and between them. J. Cell Sci. 117, 377–386. doi: 10.1242/jcs.009904

Carregano, G. E., Spanevello, A., Sabato, R., Dagnolo, A., Palladino, G. P., Beretta, G., et al. (2010). Systemic and intraoral inflammation in sleep apnea and obesity: the role of IL-1α and IL-8. Endod. Res. 135, 35–43. doi: 10.1016/j.jcdr.2009.09.004

Castillo-Bruno, P., Bihan, D., Nápoles, M., Haiman, S., Meo, M., Garcia-Arza, A., et al. (2011). A role for specific collagen motifs during wound healing and inflammatory response of fibroblasts in the latest fish gillhead seabream. J. Mar. Biol. 48, 826–844. doi: 10.1152/jn.00610.2012

Chen, M. G., Liu, Z. D., Zhou-Ching Chang, J., Huang, C. F., Chuang, F. H., Lee, J. J., et al. (2012). Regulation of vascular cell adhesion molecule 1 in dental pulp cells by interferon-beta: the role of prostanoids. J. Endod. 38, 774–779. doi: 10.1016/j.joen.2012.01.030

Christmann, R. B., Sampao, R., Fibu, G., Bocqo, C. L., DeVuvallo, C. R., Kreutz, R., et al. (2015). Key roles for interferon- and TGF-beta-regulated genes, and macrophage activation in protractive lung fibrosis associated with Systemic Sclerosis. Arthritis Rheum. 67, 2143–2153. doi: 10.1002/art.38288 [Epub ahead of print].

Dundisow, S., Hentin, M. W., and Belk, A. E. (2013). Pathologies at the nexus of blood coagulation and inflammation: thrombin in hemostasis, cancer, and beyond. J. Mol. Med. 91, 1257–1271. doi: 10.1007/s00109-013-1074-5

Dong, Y., Wang, X. B., Qian, F., Vogl, S., Xiao, L., Ranjan, R., et al. (2012). Protective role of reactive oxygen species in endothelin-induced lung inflammation through modulation of IL-10 expression. J. Immunol. 188, 5734–5740. doi: 10.4049/jimmunol.1101123

Downs, A., Baldur, D., Darby, L., and Gallina, G. (1995). Apoptosis mediates the decrease in cytokinility during the transition between granulation-tissue and scar. Am. J. Pathol. 146, 56–64.

Dwarka, S. J., Saini, S. K., Qim, Q., Hu, J. G., Yu, Y. C., Dwarka, M. N., et al. (2008). Delayed wound healing in C3HClK2 knockout mice. J. Invest. Dermatol. 131, 225–244. doi: 10.1097/00002128-200805000-00012

Duggen, B. F., and Evans, M. C. (2014). Wound healing: an overview of acute, fibrotic and delayed healing. Foren. Bioco. 7185, 278–288. doi: 10.7273/1184

Dranoff, C. A. (1986). Role of allergic bronchial asthma in tissue repair. J. Invest. Dermatol. 87, 209–215.

Dunati, L. (1995). Wound healing: the role of the macrophage and other immune cells. Adv. Vet. Sci. Comp. Med. 40, 231–240. doi: 10.1155/2002/045328-1995-00000-00015

Dunne, J. L., Collins, G. R., Brandal, A. L., Ballantyne, C. M., and Ley, K. (2003). Mac-1, but not LFA-1, uses intercellular adhesion molecule-1 to mediate slow leukocyte rolling in TNF-alpha-induced inflammation. J. Immunol. 171, 6105–6111.
Wu and Chen Linkage of inflammation and repair

Muller, A. K., Meyer, M., and Werner, S. (2012). The roles of receptor tyrosine
Morescalchi, F., Duse, S., Gambicorti, E., Romano, M. R., Costagliola, C., and Semer-
Maslinska, D., and Gajewski, M. (1998). Some aspects of the inflammatory process.
Martin, P. (1997). Wound healing – aiming for perfect skin regeneration.
Hellberg, C., Ostman, A., and Heldin, C. H. (2010). PDGF and vessel maturation.
Gregory, C. D. (2013). Inflammation and cancer revisited: an hypothesis on the
Fried, S. K., Bunkin, D. A., and Greenberg, A. S. (1998). Omental and subcuta-
Elmore, S. (2007). Apoptosis: a review of programmed cell death.
Kirsner, R. S., and Eaglstein, W. H. (1993). The Wound-Healing Process.
Hotamisligil, G. S., Shargill, N. S., and Spiegelman, B. M. (1993). Adipose expression
Hellberg, C., Ostman, A., and Heldin, C. H. (2010). PDGF and vessel maturation.
Young, K. H. (1993). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kirsner, R. S., and Eaglstein, W. H. (1993). The Wound-Healing Process.
Koike, M., and Tani, T. (1988). Tissue injury and cytokine production in human
Kirchgaessner, T., Mayr, J., Baier, C., Verl, I., Haidl, M., and Derksen, W. (2004). TGF-beta receptor type II in murine and human wound repair: expression, localization, and function. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Li, F., Huang, Q., Chen, L., Ying, Y. L., Su, R., Liu, S. Z., et al. (2010). TGF-beta type I receptor activation induces macrophage polarization and regulates neutrophil accumulation in a murine model of cutaneous wound healing. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Li, A. L., Yang, Y. Y., Gao, C., Liu, Y. J., Jeong, H. W., Liu, B. H., et al. (2015). A SAK1/AML1/IKK/IKB kinase pathway in murine and human rhytidogenesis. J.
Kammerl, S., and Faglioni, U. W. H. (1995). The Wound-Healing Process. Dermaclint, 11, 629–640.
Wu and Chen Linkage of inflammation and repair

Xing, Z., Gauldie, J., Cox, G., Baumann, H., Jordana, M., Lei, X. F., et al. (1998). IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J. Clin. Invest. 101, 311–320. doi: 10.1172/JCI32158

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