Review Article

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Physiopathology of Wound Healing in Central Nervous System

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ABSTRACT

Wound healing refers to regeneration of damaged tissue under various circumstances and activation of specific physiologic mechanisms. A wound is an immediate onset of tissue damage, contusion, or degeneration. Wounds are common pathological actions of body. After wounds happened, they should lean on healing at specific processes. Wound healing contains 4 phases initially as follows: haemostasias, inflammation, proliferation, and remodelling. Novel studies demonstrated those 4 phases with dermis wound healing process. Nevertheless, every tissue has its own healing pattern. Especially central nervous system differs from dermis in healing process. Therefore, the physiopathological wound healing mechanisms of central nervous system have been referred under novel information in this review. Healing of central nervous system is a complicated process, and the mechanisms of healing are still lacking due to several bunch of studies. Thus, clarification of underlying mechanisms of healing in central nervous system is indispensable for the sufferers.

Keywords: Wound healing, Central nerve system regeneration, Neuron, Glial scar

1. INTRODUCTION

A wound is the degeneration of normal anatomical structure and function of tissues derived from various pathology [1]. Both minor incision of skin and contusion of tendon, muscle, nerve, parenchymal organs, and bones are all could be defined as wound. Wounds in body are classified with associated tissue also origination, occurrence, containing foreign matter. Classification of wounds could be exerted as follows: internal and external wounds according to origination, acute and chronic wounds according to healing, dirty and clean wounds according to containing/not foreign matter. Wounds could be defined with one or more than one of those definitions [2].

Wound healing is a dynamic process containing different stages. Healing process involves four basic stages which refer to haemostasis, inflammation, proliferation, and remodelling (maturation). Following tissue damage, healing process begins in forementioned order. Healing phases should be completed perfectly, where one of them could not be completed healing does not occur wholly. By the way, acute wounds turn in chronic wounds depending on some circumstances such recurring frequently infections, increasing pro-inflammatory cytokines and reactive oxygen species (ROS), rising proteases levels. Decubitus ulcers and diabetic wounds could be given as example [3,4]. Excessive healing is the long period of time during the remodelling phase and healing of wound becomes permanent that phase [4]. The underlying mechanism is the overexpression of growth factors and reduced activity of metalloproteinases, consequently the tissue covered with scar. Keloids, hypertrophic scars, adhered tendons and blockage of transmission in nerves after nerve injury could be defined as [5].

1.1. Phases of Healing

The second phase is inflammatory phase which platelets, neutrophils, monocytes, and lymphocytes begin to take part in wound healing. Platelets activate the inflammatory process. Neutrophils are first arrived cells to injury area and immediately begin to defend tissue against foreign invaders and clean debris forced by neutrophil extracellular traps (NET) or phagocytosis. Monocytes the cells which have special scavengers with phagocytic properties are the next defenders following neutrophils. Monocytes also work as necrotic tissue and debris cleanser and secretes many various mediators [7]. Lymphocytes are type of cells which contribute to wound healing but there is limitless certain knowledge about their roles. There are two main types of lymphocytes, entitled B and T, which cells have different functions in wound area. In an experimental study in mice revealed that lack of lymphocytes accelerated wound healing also increased inflammation, reduced angiogenesis, and contributed the scar formation. Based on these, it was suggested that T lymphocytes imbalance inflammation and angiogenesis [8]. Moreover, it was stated that B lymphocytes were not necessarily cells for wound healing but their existing supported restoration of tissue [9].

The decrease of migrated cells during inflammatory phase, enhances wound healing. These factors could be represented in two sublines: depending and non-depending transcriptional factors. Non-depending transcriptional factors are released from the damaged cells and are transferred to ECM. Calcium waves, gradient of ROS, and purinergic factors such as adenosine, nucleotides and ATP are the main stimulators of this process. Healthy cells also could release such factors [6]. High mobility group of box-1 (HMGB1), proteins of S100, heat-shock proteins, interleukin (IL)-1α, IL-33, complement products (such as C3a, C4a, and C5a), and extracellular cell division products (such as hyaluronic acid and fibronectin) account for such molecules also called as damaged associated molecules patterns (DAMP's) [6,9,10]All these factors and migrated cells complete the phase in healing area.

1.2. Wound Healing in Central Nervous Systems

Every year millions of people suffer from traumatic brain injury which effected deleteriously the Central Nervous System (CNS). Also, 22 % of these people lose their lives in spite of treatment. Approximately half of the survival have to live with their disabilities in their entire life [11,12]formatting, evaluating, and submitting data to the Centers for Disease Control and Prevention (CDC). Similarly, it is stated that in spinal cord it is close to other parts of CSN. Spinal cord injuries (SCI) incidence and prevalence are raising too. Every year millions of people die or have disabilities which continued entire life [13,14]. In consideration, it is clear that healing process of CNS is very important. Though CNS damages are not occurred only by traumatic, it also arises from

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stroke, silent cerebral infarcts etc to CNS damages [15]. Development of damage also effects regeneration of CNS tissue. The limitation does not only depend on neuron regeneration capability but also healing process differences [12, 16].

CNS has two structural differences which are blood-brain barrier or blood-spinal cord barrier. These barriers protect CNS and prevent molecules cross over, except small and lipophilic molecules, with tight junctions. Further it makes hard to use oral or intravenous materials as a supporting agent for CNS damages. Second differentiation is that CNS has unique cells which found in three types and called as oligodendrocytes, astrocytes, and microglia. Oligodendrocytes are assigned to structure for myeline sheet and astrocytes serve on blood-brain barrier. Microglia are tissue macrophages in CNS. Those cells comprised half of the CNS cells and split CNS from other tissues in healing process [13,16].

1.2.1. Inflammation Phase

Inflammatory phase is also differs in CNS compared to other tissues in which the first phase of healing haemostasis [16,17]. It is known that blood-brain barrier damages occur in like traumatic brain damages make easy to cross over blood-brain barrier of blood cells and serum, trombone, immunoglobulin, and proteases. In addition, peripheral monocytes could easily pass over damaged area through CNS. For this reason, monocytes are dominant factors in first stage, after reconstruction of blood-brain barrier CNS support cells become more dominant [16,17].

Microglia and astrocytes are typical cells in CNS, displaying activity in inflammation phase. [16,17]. There are two types of microglia called M1 and M2. M1 type of microglia secretes some pro-inflammatory cytokines such as interferon- gamma (IFN-γ), tumour necrosis factor (TNF)-α, IL-1 and IL-12, causing inflammation. On the other hand, M2 type of microglia secretes some molecules such as IL-10, transforming growth factor (TGF)- β and suppressor cytokine signal (SOC) and tries to under control inflammation and protects neurons [18]All microglia with their secreted molecules make an afford mainly for cleaning to debris occurred in wound tissue [16,17].

Astrocytes are other type of cells displaying activity in wounded area. They have A1 and A2 phenotypes similarly names to M1 and M2. The main difference between them is C3 protein which is a member of the complementary system. Originating from here A1 astrocytes cause neuronal damage and type A2 astrocytes contribute to neuroprotection [19,20]. Activated astrocytes are astrogliosis increase glial fibrillar acidic protein (GFAP) expression level by activation. The enhancement of GFAP becomes easier that microglia make phagocytosis holding to necrotic astrocytes. Also, astrocytes contribute to immune response with nitric oxide. In addition, they have a role in organised of vessel diameter via vasoconstrictors. These all specialties of astrocytes provide second type effector immune response [16]. When evaluating astrocytes localisation in wound, it is attended that astrocytes are in peripheral areas. On the other hand, microglia and macrophage coming from blood and transforming from monocytes found at colonise situation in centre of the damaged [16].

There are two main factors, which are activated to astrocyte and microglia, in inflammation phase. First activator is thrombin [16,17]. Thrombin is a serin proteinase which exists in neurons and glial cells under normal conditions. Disruption of blood-brain barrier augments thrombin transition through CNS and cause a more boost thrombin supply. This cross over increases the release of microglia and pro-inflammatory cytokines via p-38 mitogen activated protein kinase (MAPK) and c-Jun N-terminal kinase signalling pathway. Enhancement of cytokines induce astrocyte activity. Deleterious neurotoxic release of thrombin that became neurotoxic also damages CNS either [21]. Further molecules which activates astrocytes and microglia are DAMPs and alarmin synthesized from necrotic cells [12]though the latter is often overlooked in the context of the CNS. The mere presence of immune cells in the CNS was long considered a hallmark of pathology, but this view has been recently challenged by studies demonstrating that immunological signaling can confer pivotal neuroprotective effects on the injured CNS. In this review, we describe the temporal sequence of immunological events that follow CNS injury. Beginning with immediate changes at the injury site, including death of DAMPs. Alarmins are endogenous chemotactic or immune activating proteins and peptides, expressed following cell damage or death in order to trigger immune response and process intracellular protection via pattern recognition receptor (PRRs). Alarmins replace in various tissues and counteract invader microorganisms, regulates innate inflamma-

tory response and production of inflammatory mediators, also relocate neutrophils and macrophages to eliminate microorganisms and scavenge wounded tissue. Alarmins vary according to originated areas and named as granular, cytoplasmic or nuclear [22,23]. IL-33 is one of the most important nuclear alarmins acting in inflammation and facilitates transition of monocyte originated astrocytic chemokines through CNS. One of other alarmins is ATP, which is a cytoplasmic alarmin, stimulates neutrophil chemotaxis and also a primer chemotactic for microglia [12] Other alarmins in inflammation process which regulate immune response and macrophage activity and balance intense of leukocytes, are uric acid, HMGB1 and IL-1α [22].

Glial scar formation is another difference that occurs in the inflammatory phase in the CNS and is not seen in the other tissues. [16]. It has a capsular shape which consist of reactive astrocytes, activated microglial cells and oligodendrocytes. Inside of the scar formation exist fibroblasts and fibroblast like cells. When it reframed the aspect, glial scar actually is a fibrotic scar tissue. There are two main layers in the scar formation and the layers separated with a rigid basal lamina. Inside of these two layers, activated macrophages and microglia becomes an additional layer. As a result, damages area is surrounded by three layer [24] (Figure 1). This formation prevents to digress active cells from the damaged area. At the same time, the scar formation averts spread of molecules which erupt from damaged cell or secret from cells being near of the injured area. Thus, inflammation is localized in limited area [16]. Another function of the scar formation is that it supports the blood-brain barrier via increased proliferation of astrocytes in the area. Similarly, it procures to start restorative mechanisms. Although, the scar formation has many advantages to healing, it limits the neuronal growth. The reason of the limitation is that proinflammatory and neurotoxic molecules which secret by astrocytes and macrophages, cumulation of ECM and scar formation are and function of scar formation like as a barrier [25].

1.2.2. Proliferation Phase

The proliferation phase starts after inflammatory phase through TGF-β ,that especially releases macrophages, leading to secretion of cytokines [16]. In the phase, glial scar induces to release of cytokines and provides to clean series of molecules spreading damaged tissues by glutamate. Although this process seems to be useful, glial scar formation restricts to regeneration. Molecules secreting from around of the scar reduces axonal regeneration. The molecules are classified as glial related molecules and myelin related molecules. Neural/glial antigen (NG) 2, phosphocane, EphB2, tenacin-C and semphorin 3A are included in the inhibitor molecules.

Another property of proliferation phase is that astrocytes ECM secretion. Astrocytes accelerate the secretion of ECM with main components such as chondroitin sulphate proteoglycans (CSPG) and heparan sulphate proteoglycans (KSPG) [26]. In this stage, ECM reorganisation starts addition of the accelerated ECM production. When the reorganization and scar structure are evaluated, it is mentioned that granulation formation begins. The formation is termed as granular view, and it is a primitive tissue consisting of new blood vessels, fibroblasts, inflammatory cells, and new produced ECM members. Sometimes the granular formation is accepted a sign of the healing. It is determined that after spinal cord injury beings at a part of the CNS, the formation exists. Against to that, the granulation tissue is shown as prolonged healing in other part of CNS. However, it is accepted that the formation is a structure for neuronal progenitors which contribute to tissue healing, similar to partial granulation tissue in other tissues [27].

Addition of mentioned situation in that phase, increase of ECM in the area limits neuronal regeneration. It is asserted that originated inhibition is ensured by mainly chondroitin sulphate proteoglycans. [16,17,28] Also, molecules such as NogoA, Ephrin (Eph) A4/A5, CSPG, phosphatase and tensin homolog (PTEN), SOC-3 have a role in the inhibition of axonal growth. It is alleged that Eph4 is the most important molecule among them and is affected by supressing the activity of Rho-associated kinase activity [26].

1.2.3. Remodelling Phase

Remodelling phase starts with contraction for restitution and gradual shaping in damaged area. In that way, injury area is tried to be fixed because of glial scar and inhibitor molecules, regeneration is insufficient. Thus, a gap occurs inside of the glial scar in the area. The gap is replenished by type I, II and IV collagen, fibronectin and laminin secreted from meningeal fibroblasts [16,17].

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A theory, which put forward by Cajal, assumed that if improvement stops, it does never continue because of complexity of nervous system. At that point, it is considered that restricted regeneration is possible, although it is not existed to expect [29]. Brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), casein kinase (CK) 2, growth-associated protein 43 (GAP43), TGF-β and Kruppel-like factor (KLF)-7 are molecules which play a critical role in the continued limited regeneration process [26].

BDNF, a member of the neuronal growth factor (NGF), is the most expressed neurotrophin in the mammalian brain. BDNF display its activity through tropomyosin receptor kinase (Trk) B and another low-affinity receptor p75NTR. Even so TrkB is the main pathway to BDNF. Through the pathway, BDNF protects neurons from apoptosis. Its happen with suppressing the apoptosis via apoptotic proteins' regulation and at the same time with increasing the pro-survival genes transcription which is related to cyclic AMP response binding protein (CREB) [30,31]. BDNF roles to neuronal development, neuroplasticity and remyelination. It is reported that BDNF realize the functions after the injury. [32,33]. Another molecule having a role in regeneration is VEGF. VEGF is secreted by target tissue in hypoxia. There are different types terming VEGF-A, -B, -C, -D, E (virally encoded), and placental growth factor (PIGF) [34,35]. VEGF- A is the most researched form of these types. VEGF-A has both pro-angiogenic and neuroprotective effects. Despite VEGF-A causes destruction of the blood-brain barrier and vascular effluence, it is known that it induces to neurogenesis in proliferation phase [36]. In addition, these two molecules, CK2 has a role in proliferation phase. CK2 being multifunctional and well-protected enzyme is a member of the casein kinase family which is serine/threonine protein phosphotransferase. It has several functions including affecting neuronal differentiation, taking charge in growth process, occurring the growth cone and making synaptic connection formation [37]. If it is expressed during injury, it has neuroprotective effects. Besides, it is reported that if it synthesis from glial cells, it could be reduce neurotoxicity in the cause of AMPA [38]. Different molecule being related with proliferation phase is GAP-43. It is also known as neuromodulin. The molecule is expressed in perinatal period noticeably and its quantity reduces in progress of time. It is established that GAP-43 are found intensively in granular cells of the cerebellum, neocortex, entorhinal cortex, hippocampus, olfactory bulb, and retinal cells. GAP-43 has chemical specialties and contact with various presynaptic molecules; therefore, it promotes plasticity and neuronal growth. Moreover, it impacts through inhibiting Nogo-AN/Nogo 66 which is a molecule related with inhibitor process. All these roles, GAP-43 is one of the important molecule for remodelling phase and it is paid attention as a potential therapeutic molecule [39]. The molecule of providing to end inflammation phase TGF-β has a role at the same time in the proliferation phase. It is expressed being different three isoforms

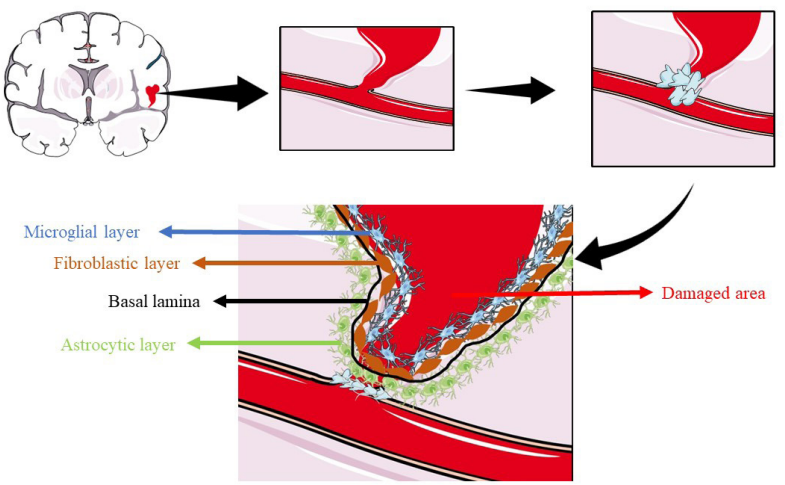

Figure 1. Schematic demonstration of glial scar formation.

from neurons, astrocytes, and microglia. Its effects to reducing inflammation and increasing survival of cells. These effects increase the apoptosis and also induce proliferation and differentiation. Additionally, in the researches it was presented that TGF- β stimulates early leaving from cell cycle to progenitor cells and enhances CREB levels in hippocampal neurons. [40–42]. KFL7 is a worth mentioning molecule which relevant in this phase. It is a member of the Kruppel-like factors family. KFL7 with other family members is involved in physiologic and pathologic several events which include proliferation, differentiation, and cell death. Its mission in healing process after damage is especially related with neuronal survival and axonal regeneration [43].

Remodelling is difficult situation, and it is acknowledged that replacement of scar tissue into new neurons is nearly impossible involving healing process of CNS. However, mounted evidence suggest that new cells are ingenerated in CNS. It is reported that immigrating from subventricular and subgranular areas including hippocampal and olfactory regions these cells act under normal conditions. Also, it is alleged that they could immigrate to damaged areas after ischemia and stroke. Although these findings, it is not clear that whether this migration will be functional [16,44,45].

2. CONCLUSION

Healing response in CNS become in four main phases similar to classic healing. In the first phase of haemostasis, coagulation and restoration of blood-brain barrier begin. The phase is finished whit development of hypoxia with plasma proteins. In the second phase of inflammation, microglia and astrocytes activation and leukocytes are infiltrated. Thus, debris are cleaned by these cells. These two phases generally take approximately during seconds to hours. However, it was reported that the time could be prolonged until days in some cases. In the third phase of proliferation, scar tissue is reorganized, ECM is produced, and partial granulation tissue is maintained. The phase's period starts two hours after damage and could be possible that it continues for about ten days. In the last phase of remodelling, scar tissue is reorganised, and neurons are regenerated as far as possible. Remodelling phase duration is the longest among of other phases. It starts first week of the injury and continues to weeks, even it could be prolonged till a year [27,46] (Figure 2).

All in all, healing in CNS is a process separated from other tissues and has some unique properties. Because of existing numerous cell and molecule which are effective on healing process of the CNS, it is nec-

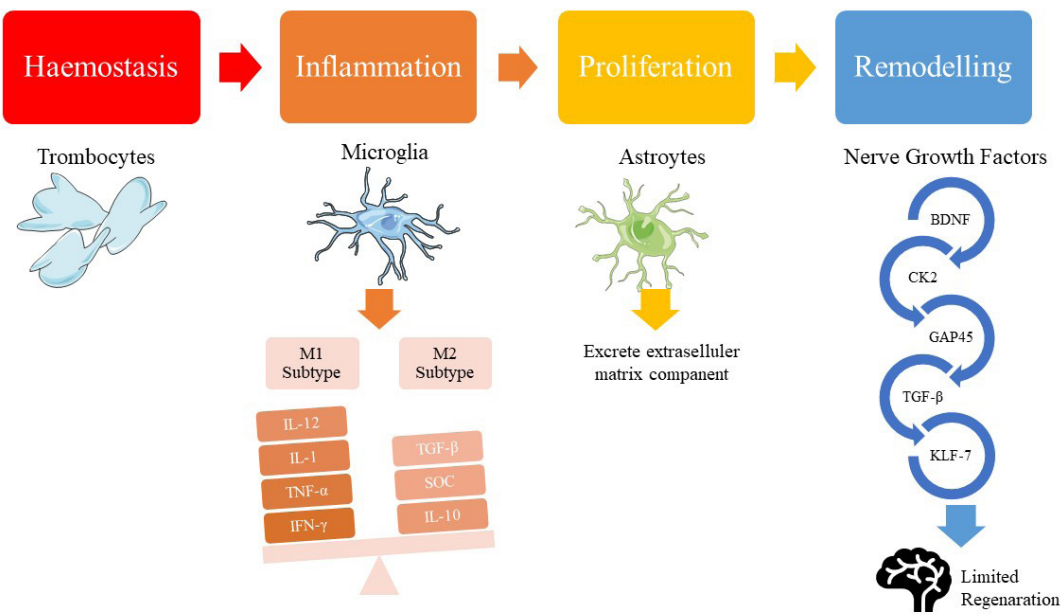

Figure 2. Representative scheme of the healing process in CNS.

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essary to investigate of these healing process and related molecules. Achieved results after research will contribute to the understanding of the process and improvement of therapeutic agents.

Conflict Of Interest

The authors declare that they have no conflict of interest.

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Author Contributions

Each author contributed equally.

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