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Regeneration and Cicatrization

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Abstract

Cicatricial tissue, being the local center of sclerosis, replaces the wound or focus of cell death. Scarring is caused by various types of injuries, including operations, as well as by a number of diseases. Scarring often culminates in the formation of strictures and other complications. Integrated stimulation of regeneration that takes the role of the immune system into account, in conjunction with the prescription of enzyme preparations possessing proteolytic activity, can be used to reduce the severity of sclerosis of damaged tissues.

Keywords: cicatrization, regeneration, pluripotent stem cells, immune system, testosterone

Introduction

Cicatricial tissue, being the local center of sclerosis, replaces the wound or focus of cell death [1]. Scarring is caused by various types of injuries, including operations, as well as by a number of diseases. Scarring often culminates in the formation of strictures and other complications [2]. In the case of injury, the ratio of fibroblasts and progenitor cells coming to replace dead cells determines the severity of the formation of fibrous tissue. When there is migration of a sufficient number of progenitor cells of an epithelium and other tissues, and with adequate replacement of dead cells by progenitor cells, the cell death site can fully recover without the development of fibrous tissue. In contrast, under conditions of an insufficient amount of progenitor cells coming to the cell death site, and the inability to complete regeneration of the given tissue site, the increase in the level of cellular growth factors aimed at stimulating progenitor cells causes intensive proliferation of fibroblasts. Fibroblasts begin to predominate over the progenitor cells entering the damage zone, resulting in the formation of a scar [3, 4].

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Under cell death and the concurrent inflammation, macrophages, as well as the surrounding epithelial and endothelial cells, and stromal cells of hematopoietic and lymphoid organs, form cell growth and colony-stimulating factors, and interleukins [1, 5]. Cell growth factors, acting in various combinations, selectively stimulate the proliferation and differentiation of progenitor cells of an epithelium and other tissues [6]. Colony-stimulating factors induce pluripotent stem cell proliferation [6] for their subsequent replenishment of progenitor cells of an epithelium and other tissues and entrance into directly into places of cell death [3]. Management of the differentiation processes is carried out by the relevant part of the development program, which initiates the formation by the local cellular environment of cell growth factors in a strict sequence, as well as the appearance of complementary receptors in precursor cells [3, 7, 8]. Every cell in a multicellular organism contains a certain set of surface receptors that enable it to respond to the corresponding set of signaling molecules, as well as communicate with other cells and the extracellular matrix. This set of receptors is a "morphogenetic code" which defines the organization of cells in tissues [6]. The strict sequence of the appearance of the expression of receptors to cell growth factors and the same strict regulation of formation of (autocrine or paracrine) cell growth factors themselves at different stages of cell differentiation confirms this conclusion [3, 4]. An example can be seen in the monograph by Roitt I. et al. (2000) [9] that presents the alternation of receptor expression to different growth factors during the differentiation of T- and B-lymphocytes. Incretion of cell growth factors continues until the full restoration of damaged tissue or the formation of fibrous tissue activated by fibroblasts at the site of the injury. After the replacement of old dead cells with new cells, local production of cell growth and colony-stimulating factors ceases [3, 4, 10].

Committed stem cells (tissue-specific stem cells) migrate to tissue specific antigens of proteoglycans of fibronectin (part of the basal membrane, converts to the extracellular matrix) that are complementary to their receptors. The basal membrane does not prevent the migration of a macrophages and committed (tissue-specific) stem cells which support regeneration. After passing through the basal membrane, committed (tissue-specific) stem cells bind their tissue-specific receptors bind to their complementary antigens of proteoglycans of laminin (part of the basic membrane, converted to the epithelial layer), and are retained in the epithelial layer. Committed (tissue-specific) stem cells keep their connection with the basal membrane also keep contact with the underlying connective tissue, which executes control over differentiation of epithelial cells. The direction of differentiation of migrated committed (tissue-specific) stem cells is determined by the specific set (corresponding to the morphogenetic code) of cell growth factors on fibronectin and laminin of the basal membrane, as well on collagen fibrils of the extracellular matrix [3, 6, 10].

The intensive formation of cell growth factors that stimulate the proliferation of endothelial cells (vascular growth factor and others), leads to proliferation of endotheliocytes, and the formation of new blood vessels (angiogenesis) at the injury site. The endothelium, in turn, under inflammation, produces basic fibroblast growth factor and others cell growth factors, which intensify proliferation with formation of granulation tissue, and lead to formation of IL-7, which causes the expression of Bcl-2. The expression of Bcl-2, which increases resistance to cell death by apoptosis [5, 11], protects the endothelium, migrating stem cells and fibroblasts from the highly active products of cytotoxic cells and macrophages at the site of inflammation [3].

Fibroblasts are involved in the formation of specialized architectonics of the connective tissue that corresponds to its local functions [8]. Due to the activity of fibroblasts, an extracellular matrix is produced containing type I and type III collagens. Most types of connective tissue are made up of these types of collagen. As the cicatrice matures, the ratio changes towards type I collagen. The basis of immature argyrophil collagen fibers is type III collagen [12]. Accordingly, when there is an increase in the levels of cell growth factors and an increase in their stimulation of proliferation of fibroblasts, type III collagen begins to predominate in the forming connective tissue [3].

When there is prolonged exposure to a particular stimulus, desensitization of the corresponding

receptors in target cells develops [6]. Therefore, under violation of regeneration, a consequence of the concomitant increase over long periods of cell growth factor levels, aimed at stimulating division of progenitor cells of an epithelium and other tissues, is desensitization of their receptors [3]. For example, fibroblasts taken from patients with Werner's syndrome (a syndrome of premature aging caused by the violation of regeneration), are insensitive to fibroblast growth factor and some other cell growth factors [6].

The excessive stimulation of fibroblasts by cell growth factors, the increased levels of highly active products of cytotoxic cells and macrophages (TNFα, respiratory explosion products), as well as peroxidation products, cause degenerative changes in fibroblasts by reducing their size and causing the appearance of deformed and hyperchromatic nuclei during inflammation at the injury site. These changes lead to disruption of the structure of the connective tissue and to an increase in the proportion of immature argyrophil collagen type III fibers. Collagen and elastic fibers become thinner and more branched – their thickness decreases and there is an increase in their number of oblique cross-sections [3]. The change in the structure of the extracellular matrix adversely affects the regeneration process, leading to disruption of cell migration and intercellular signaling [4, 6, 10].

The collapse and replacement of collagen and other extracellular matrix macromolecules occurs continuously under normal conditions. Collagens are cleaved by specific extracellular enzymes – collagenases [6]. Drugs with proteolytic activity (Longidaza, Fermencol, and others), complementing the natural mechanisms of regeneration of connective tissue [13], show similar selective activity with respect to branched molecules of the pathological collagen with junctional and vortex stacking of fibers (characteristic of keloid and hypertrophic scarring), and are less active in relation to the collagen fibers of normal connective tissue. Under the influence of drugs with proteolytic activity, there is a reduction of the scar size as a result of lysis of excess pathologically altered collagen fibers [14]. For this reason, for prevention of fibrosis at the site of the damage, the patient should be given a drug with proteolytic activity as part of combination therapy [4].

When tissue is damaged, it is not enough to terminate the action of the damaging agent and lysis of necrotizing cells for the tissue to be restored. It is also not enough for restoration of the tissue site of lysis already formed on the site of sclerosis. In the latter case, the prescription of enzymes having proteolytic activity will only lead to resumption of paracrine formation of cell growth factors to repair the reintroduced defect [4]. Under the conditions of inadequate entry of progenitor cells to the place of the lysed scar due to depletion of their cellular composition or because of damage to the extracellular matrix, the renewed paracrine production of cell growth factors will lead to stimulation of fibroblast proliferation and to scarring relapse [3, 4].

The Role of Pluripotent Stem Cells in Regeneration

Cells renewal can occur through simple division to form two daughter cells of the same type, or through progenitor cells. During cell division, progenitor cells of an epithelium and other tissues form a progeny, some of which continue to differentiate, while another part remains poorly differentiated [6]. At the same time, progenitor cells and differentiated cells, having embarked on the differentiation path, or completing it, can divide only a limited number of times [6] and are not able to provide tissue regeneration throughout the entire ontogeny [3]. Renewal of tissues over such a long period is impossible without the participation of a specialized system responsible for regeneration. Pluripotent stem cells are an integral part of this system, and can migrate and differentiate into all types of somatic cells and germ line cells, and have the ability to self-renew throughout the life of the organism [3]. Formation and renewal of tissues, carried out by the migration of cells, is a more complicated process compared to dividing of cells-founders. Formation and regeneration of tissues, carried out by migrating cells, is widespread in nature, including the various stages of human ontogenesis [6, 7].

Pluripotent stem cells are a separate branch of the differentiation of embryonic cells [6], which provides regeneration of all body tissues during ontogeny [3].

The universality of the recovery mechanism implemented by pluripotent stem cells is confirmed by the gradual replacement of cells of all of the recipient's tissues with the donor's cells after transplantation of peripheral blood pluripotent stem cells with pre-conditioning conducted in hematological patients [3].

Affirmation of the universality of the regeneration mechanism implemented by pluripotent stem cells comes from the long-term results of local radiation exposure, in which, in spite of the cell death of the progenitor cells, the percentage of irreversible late radiation damage is relatively small, and does not exceed 5% [15]. Only restoration of the progenitor cells of an epithelium and other tissues thanks to migration of tissue-specific stem cells can prevent irreversible changes in this area [3].

Given that in the experiment dissociated cells more easily aggregate with analogous cells, pluripotent stem cells are more aggregated with poorly differentiated progenitor cells of an epithelium and other tissues, adding to their number. The subsequent cell differentiation of progenitor cells contributes to the replacement of dead cells. The basement membrane underlying the epithelial layer does not prevent the migration of macrophages and tissue-specific stem cells through it. Tissue-specific stem cells add to the number of poorly differentiated progenitor epithelial cells and progenitor cells of other tissues, in turn providing a replacement for dead cells. Cells that maintain contact with the basement membrane also keep contact with the underlying connective tissue, which conducts control over the differentiation of epithelial cells [6, 8].

The direction of migration of stem cells is given by the formation in these cells of tissue-specific receptors over several stages. Initially, antigen presenting cells (macrophages, etc.) bind with tissue-specific antigens from dead cells. Antigen presenting cells deliver tissue-specific antigens from dead cells to the lymph nodes or other lymphoid organs of T-helper cells [3, 5]. After an analysis of the antigens received, T-helper cells use antigen-presenting cells as mediators (increasing the likelihood of a meeting between constantly circulating cells) to activate the pluripotent stem cells/T-killer cells, with formation of tissue-specific receptors on their surface that determine the place of their subsequent migration [3]. The presentation of antigens of virus-infected cells or antigens of foreign tissues results in the activation of T-killers [5], while the presentation of autoantigens of cells that died during injury, or of old cells, leads to the activation of pluripotent stem cells with their subsequent direction at recovery of the corresponding tissue [3]. T-helper cells adhere to endothelial cells of postcapillary venules, squeeze between them, and then migrate to the lymphatic vessels, through which they enter the lymph nodes. This path is also used by T-killers [6] and pluripotent stem cells [3]. Activation by T-helpers of T-killers is accompanied by paracrine and autocrine IL-2 formation, initiating the expression of Bcl-2 to protect the activated T-killers against apoptosis [5]. Likewise, after contact with T-helper cells through Bcl-2 expression, the development of apoptosis is prevented in stem cells, which are highly sensitive to adverse conditions of the medium, and which migrate to the damaged area or the area of destruction of old cells, and are exposed to highly active products (active forms of nitrogen and oxygen, TNFα, INFγ and others) that form under inflammation [3]. Additionally, the expression of Bcl-2 in committed (tissue-specific) stem cells is induced by IL-7, produced by endothelial cells, between which stem cells migrate. The participation of T-helper cells in the process of tissue renewal [3] determines the high prevalence of auto-antigens (99%) among the peptides presented to T-helper cells and analyzed by them, as well as a significant predominance of the subpopulation of $CD4^+$-lymphocytes (T-helpers) over $CD8^+$-lymphocytes (T-killers) in the blood and lymph [5]. Accordingly, management of regeneration processes is a leading (main) function of the immune system [3, 4, 10]. The participation of antigen presenting cells and T-helpers of the immune system in the formation of tissue-specific receptors in pluripotent stem cells for subsequent tissue regeneration is further confirmed by the following examples.

Blocking of osteoclasts (macrophages), as antigen presenting cells, when using bisphosphonates violates the presentation of antigens of old cells of bone tissue to T-helpers for the formation of the corresponding tissue-specific receptors in stem and tumor cells (which follow the same path as pluripotent stem cells when regenerating tissue) [3]. Accordingly, the effect of bisphosphonates is achieved by blocking the

mechanism of migration of stem and tumor cells when replacing old dead bone tissue cells. Violation of the natural mechanism of regeneration of bone tissue with lysis of osteoclasts of dead old cells when using bisphosphonates is accompanied by the formation of sequesters consisting of non-phagocytosed conglomerates of dead old bone cells [3].

The selective damage of T-helper cells in patients with AIDS prevents the formation of specific receptors in pluripotent stem cells. Information of antigen presenting cells bearing tissue-specific antigens is not read and is not converted into the corresponding receptors of pluripotent stem cells. Under these conditions, the majority of pluripotent stem cells, not having tissue-specific receptors, remain unsolicited, and subsequently die. In patients with AIDS the process of replenishment of the progenitor cells of an epithelium and other tissues is disrupted, which makes an additional negative contribution to the development of exhaustion, dementia and tumors [3].

Application of Chemoattractants and Other Medicines for Regeneration Stimulation

Stimulation of regeneration can significantly improve the effect of regeneration, while also reducing the scarring of damaged tissue. One of the components of this process is to encourage the formation of pluripotent stem cells. Taking the participation of pluripotent stem cells in the regeneration process into account, the comprehensive treatment of the patients should include Methyluracil as a stimulant of leukopoiesis. It would be possible to use colony-stimulating factor drugs, or immune modulators for this purpose, thereby initiating the formation of colony-stimulating factors by macrophages and other cells (medicines containing microbial lipopolysaccharide: Pirogenal, Prodigiozan, and others, as well as autohemotherapy, a form of which is cupping), but Methyluracil, with its high effectiveness, has less severe side effects. Thus, preference may be given to Methyluracil [4].

In order to stimulate regeneration and prevent sclerosis in the place of damage, pharmaceuticals can be used that contain chemoattractants (attracting antigen-presenting cells - macrophages) with xenogeneic antigens similar to antigens of damaged tissues. The use in humans of drugs prepared from different xenogenic tissues, under mediation of antigen-presenting cells and T-helper cells, leads to the formation among pluripotent stem cells of receptors complementary to the respective tissue antigens, and then to a directed migration of stem cells into tissues, the cells of which contain similar tissue-specific antigens (promoting regeneration of these tissues). There is a redistribution of migration of stem cells primarily to the place of damage [3]. Such drugs are not required to be applied locally to the injury site. These drugs include a variety of preparations made from different xenogenic tissues (liver, prostate, cartilage, cornea, etc.). They stimulate the regeneration of human tissues [16] with shared antigens (formed at similar stages of phylogeny) [4]. For the same reason, in experiments on rats with cross-circulation, liver damage in one of them leads to the stimulation of liver regeneration in both animals [6].

In order to attract macrophages and other antigen presenting cells, chemoattractants may be used locally that do not have common antigens with the damaged tissue. The macrophages attracted by these chemoattractants, finding themselves in the place of damage, phagocytose dead cells, and then present their antigens to T-helper cells, which in turn form the corresponding tissue-specific receptors in pluripotent stem cells involved in regeneration of the damaged tissue site. An oil propolis extract can be used as such a chemoattractant. Propolis consists of wood resins collected and fermented by bees. Wood resins and mineral oils are widely used in medicine in order to achieve an anti-inflammatory and regenerative effect. For example, tar and ichthyol are part of ointments used in dermatology as a “permissive” for various inflammatory processes. Tar is a major component of the famous Vishnevsky ointment. Unlike tar and ichthyol ointments, oil extract of propolis, having a comparable effect, has a pleasant aroma and is allowed for intracavitary application. Accordingly, preference may be given to a propolis preparation for stimulation of local regeneration [4].

Attracted by chemoattractants (wood oils, mineral oils, and others), macrophages not only function as

antigen-presenting cells, but also lyse the detritus at the injury site using their hydrolytic enzymes, as well as the pathologically changed connective tissue. The action of hydrolytic enzymes of macrophages not only differs by its selectivity towards altered connective tissue, but may also have expression that exceeds the effect of pharmacological agents with proteolytic activity. Confirmation of this conclusion comes from the ability of osteoclasts (generated from monocytes, and being a variety of macrophages) to destroy the bone matrix during bone tissue regeneration [6]. Macrophages of the zone of perifocal inflammation, releasing hydrolytic enzymes, lyse the surrounding tissues (destroy the endothelium, basal membranes, fibronectin, collagen, elastin, bone matrix and other structures), making room for new cells, as well as fibroblasts when there is an insufficient entry of the latter [5]. Macrophages located on the periphery of a malignant tumor possess a similar capability. These macrophages are able to lyse almost any tissue using their hydrolytic enzymes, freeing space for cells of the growing cancerous tumor [3].

An unchanged intercellular matrix is a prerequisite condition for completion of regeneration. It is necessary for the migration of young cells, and its connective tissue provides the direction for the further differentiation of these cells and intercellular signaling [6]. Prescription of hyaluronic acid can improve the conditions for migration of stem cells through intercellular space, and thereby stimulation of regeneration. Hyaluronic acid represents one of the groups of glycosaminoglycans. Attracting water, and thereby causing swelling of the extracellular matrix, hyaluronic acid creates conditions for cell migration and regeneration [6]. Additionally, for the same purpose, the patients should be prescribed glucosamine orally. The selectivity of the action of drugs with proteolytic activity directed predominantly at lysis of pathologically altered connective tissue makes it possible to use these drugs in conjunction with glucosamine and hyaluronic acid preparations, which can improve the conditions of the migration of stem cells to the site of injury [4].

Ca^{++} and Mg^{++} are involved in the differentiation of cells and in the spatial organization of tissues, and affect intercellular adhesion mechanisms [6]. They thus create the conditions for regeneration of damaged tissues. For this reason, the patient should be prescribed a comprehensive preparation of vitamins and minerals [4].

The Negative Influence on Regeneration of a Decrease in Pluripotent Stem Cells and Sexual Hormones in People over 35-40 Years Old and Other Factors

To restore the damaged tissues, there needs to be constant replenishment of progenitor cells of an epithelium and other tissues by the necessary quantity of tissue-specific stem cells, which are transformed into progenitor cells and then differentiated cells (instead of dead cells) under the influence of the cellular environment [4]. A whole series of factors have a negative effect on the regeneration process.

Entry to the damaged area of the required number of stem cells is provided for by adequate vascularization of the damaged tissue site [3]. In contrast, impaired microcirculation and blood supply (e.g., under excess tension in the tissue in the region of the surgical incision) leads to the death of even greater numbers of cells at the site of damage from developing ischemia, and simultaneously, to a reduction in the entry of tissue-specific stem cells and progenitor cells to this region. Intense scarring of tissue in this area and the development of related complications are a consequence of the growing imbalances between progenitor cells and fibroblasts in favor of the fibroblasts [4].

After 35-40 years of age, the numbers of the pool of pluripotent stem cells and progenitor cells of an epithelium and other tissues that they replenish, are reduced [3, 17], which makes it impossible to replace old dead cells with an adequate number of poorly differentiated progenitor cells or directly migrated stem cells [3]. The numbers of the pool of pluripotent stem cells after 35 years of age go down by 1% per year, leading to systemic changes [3]. For this reason, among people over 35-40 years of age, sclerosis in most tissues and organs develops with an intensity equal to the rate of the decrease of the pool of pluripotent stem cells – by 1% per year [3, 18]. The formation of cell growth factors occurs in inverse proportion to the density of the cell population [6].

For this reason, in response to the destruction of old cells and their lack of replenishment by young cells, there is an increase in production by epithelial and endothelial cells and macrophages of cell growth factors (for stimulating proliferation of poorly differentiated progenitor epithelial cells and progenitor cells of other tissues) and colony-stimulating factors (for stimulating proliferation of pluripotent stem cells) [3]. Despite the development of these compensatory reactions in people after 35-40 years of age, the pool of pluripotent stem cells and progenitor cells of an epithelium and other tissues continue to decrease, managing less and less to replace old dead cells. With increasing age, production of cell growth factors aimed at stimulation of cell proliferation and an increase in the number of progenitor cells of an epithelium and other tissues naturally increases. Excess, increased mitogenic stimulation, which increases proportionally to age, is observed in all tissues in people older than 35-40 years of age, leading to activation of fibroblasts and their formation of fibrous tissue [3]. Accordingly, in people over 40 years of age, the intensity of sclerosis at the site of tissue damage increases. To reverse the development of pathological processes associated with the violation of regeneration in individuals older than 40 years of age, there needs to be restoration of numbers in the pool of pluripotent stem cells [3]. To do this, transfusing mononuclear fraction of peripheral blood harvested from young donors 18-23 years old with the same blood group and sex as the recipient, and containing pluripotent stem cells (Russian Federation patent number 2350340), can be used [3, 4, 10, 19].

The age-related decrease in pluripotent stem cells has a negative effect not only on the settlement of the thymus with lymphoid elements, but also on the support of the normal functional status of cortical and medullary substances of the thymus, including epithelial-reticular cells. The age involution of the thymus is accompanied by a decrease in its mass, as well as by the replacement of the thymus by joining tissue and fibroblasts products – adipocytes [5]. After 50-60 years of age there is a decline in the quantity of T-helper cells in the blood, which adversely affects the formation of tissue-specific receptors among stem cells, necessary for the regeneration process [3]. Despite this, stem cells continue to enter the thymus throughout a person's life, and mature T-cells continue to migrate from the thymus [5].

A long-term chronic inflammatory process can lead to sclerosis of tissues. The long duration of alteration factors, the death of a large number of cells caused by these factors, and the correspondent formation of cell growth factors that stimulate proliferation of not only progenitor cells, but fibroblasts as well, and blocking the development of apoptosis of fibroblasts through the expression of Bcl-2 [3], are the main pathogenetic factors for the development of fibrous tissue during the chronic inflammatory process [4].

The reduced production of sex hormones after 35-40 years of age also causes a number of negative consequences. The reduction in the formation of testosterone in men after 40 years of age gives rise to so-called partial androgen deficiency among aging men (PADAM). The age-related decline in testosterone production and, to a large degree, the development of metabolic syndrome (X - syndrome) initiated by this decline, has a significant effect on the factors of the extracellular medium that regulate cellular aging [13, 20]. For example, in normal mouse embryo cells (capable of dividing without signs of aging under the appropriate conditions), adding serum into the bloodstream of elderly individuals leads to the development of apoptosis [6]. Two of the major inducers of apoptosis are glucocorticoids and tumor necrosis factor-α (TNFα) [5], the levels of which are elevated during PADAM [13, 20].

Sex hormones are necessary for the division and differentiation of cells having receptors complementary to them. Under an age-related decrease in production of sex hormones, atrophy of tissues consisting of such cells develops, with depletion of the poorly differentiated progenitor epithelial cells and progenitor cells of other tissues and violation of replacement of old dying cells in them. To make up for the insufficient mitogenic action of testosterone, a group of compensatory-adaptive reactions is formed on the endocrine, paracrine and autocrine levels [15, 20, 21]. These compensatory reactions are aimed at stimulating proliferative activity. They include increased incretion of cellular growth factors (bFGF, IGF-I, EGF and others), an increase in levels of 17β-estradiol and 5α-dihydrotestosterone, increased formation of endocrine

activators of cell division (growth hormone, insulin, vitamin D), and other factors [20, 22]. An increase in mitogenic activity (aimed at maintaining the division and differentiation of cells bearing receptors of sex hormones) against the background of depletion of progenitor cells leads to stimulation of fibroblast proliferation and the formation of fibrous tissue at the injury site [3, 23]. Accordingly, after 40 years of age in men and women, the development of sclerosis of damaged tissues prevails over regeneration. Therefore, in patients over 40 years old with various tissue lesions, it is expedient to prescribe supplemental hormone replacement therapy (androgen replacement in men, and pregnenolone, tibolone replacement in women) in order to reduce the severity of scarring, as well as to prescribe therapies aimed at restoring the numbers of the pluripotent stem cell pool [4, 10, 13, 24].

Conclusion

Comprehensive stimulation of regeneration taking into account the immune system's role in this process, together with prescription of enzyme preparations that have proteolytic activity, can be used to decrease the expression of sclerosis on damaged tissue sites.

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