Wound healing reaction: A switch from gestation to senescence

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Abstract

The repair of wounded tissue during postnatal life could be associated with the upregulation of some functions characteristic of the initial phases of embryonic development. The focusing of these recapitulated systemic functions in the interstitial space of the injured tissue is established through a heterogeneous endothelial barrier which has excretory-secretory abilities which in turn, would induce a gastrulation-like process. The repair of adult tissues using upregulated embryonic mechanisms could explain the ubiquity of the inflammatory response against injury, regardless of its etiology. However, the early activation after the injury of embryonic mechanisms does not always guarantee tissue regeneration since their long-term execution is mediated by the host organism.
for the inflammatory processes induced by other types of adverse conditions\textsuperscript{[4,12]}. The human diseases that are associated with these conditions, including atherosclerosis, asthma, type 2 diabetes and neurodegenerative diseases, are all characterized by chronic low-grade inflammation\textsuperscript{[7]}. However, human aging can be explained by the emerging concept of inflamm-ageing, i.e., a combination of inflammation and aging\textsuperscript{[8]}. Inflamm-ageing seems to favor the onset of typical age-related diseases like atherosclerosis, dementia, osteoporosis and cancer\textsuperscript{[8]}. Inflammatory mechanisms are also involved in physiological processes, like physical exercise, embryonic development and gestation, and indeed there is the hypothesis that the evolution of the living species could be based on inflammatory remodeling of organisms induced by environmental factors\textsuperscript{[9,10]}. It has also been proposed that, although fibrosis is often initially linked to a strong inflammatory response, there are specific mediators and pathways contributing to the pathogenesis of fibrosis that are distinct from the mechanisms driving inflammation. Thus, it is assumed that to design effective therapy for fibrotic diseases, we need to begin viewing fibrosis as a pathological process distinct from inflammation\textsuperscript{[11]}.  

PHASES OF THE SKIN WOUND HEALING REACTION
The multiple pathophysiological mechanisms that overlap during the progression of the skin wound healing reaction may explain the lack of consensus on the number of phases involved in this reaction. Thus, the common description of the wound healing evolution includes three classical stages: the inflammatory phase to contain the injury and prevent infection; the proliferative phase characterized by new tissue formation, i.e., granulation and epithelial tissues; and the remodeling phase with extracellular matrix reorganization\textsuperscript{[11,12]}. However, some authors describe four healing phases: hemostasis and coagulation, with the formation of a provisional wound matrix; inflammation with neutrophil and monocyte recruitment; proliferation and repair, with the formation of granulation tissue and the restoration of the vascular network, as well as re-epithelialization; and remodeling that occurs from day 21 to up to 1 year after injury. In this phase, collagen III, which was produced in the proliferative phase, is now replaced by collagen I and the acute wound metabolic activity slows down and finally stops\textsuperscript{[1,13]}. Additionally, five phases of the wound healing reaction have also been described: hemostasis; inflammation; cellular migration and proliferation; protein synthesis; and wound contraction and remodeling\textsuperscript{[10]}.

In the above-mentioned descriptions of the wound healing reaction, the role attributed to inflammation is very limited and noteworthy. On the contrary, we have proposed an inflammatory etiopathogenic hypothesis of the wound healing evolution. According to this idea, inflammation could be the basic mechanism that drives the nature of the different stages of wound repair\textsuperscript{[15]}. Likewise, inflammation could facilitate the integration of the pathophysiological mechanisms involved in the different phases of wound repair by scar formation\textsuperscript{[15,16]}. In essence, the post-traumatic local acute inflammatory response is described as a succession of three functional phases of possible trophic meaning to the wounded tissue: nervous or immediate with an ischemia-reperfusion phenotype; immune or intermediate with a leukocytic phenotype; and endocrine or late with an angiogenic phenotype\textsuperscript{[15,16]} (Figure 1).

In turn, we have suggested that these phenotypes could represent the expression of trophic functional systems of increasing metabolic complexity\textsuperscript{[17]}. Therefore, it could be considered that, after the injury, the metabolic ability of every phenotype would be conditioned by the biochemical mechanisms used to provide the energy sources for cell functions\textsuperscript{[15,17]}. These three inflammatory phenotypes hypothetically expressed in the traumatized tissue during tissue repair by scarring could help to integrate the etiopathogenic mechanisms expressed in each evolutive phase. In this way, these inflammatory phenotypes would associate the genetic factors, upregulated and/or downregulated, with metabolic, functional and histological alterations\textsuperscript{[17]}. The interstitial space is the battle field where the inflammatory response takes place. In the successive phases of the inflammatory response, the interstitial space of the injured tissues is successively occupied by molecules, inflammatory cells, bacteria and finally by a mesenchymal-derived tissue, the granulation tissue. In summary, the inflammatory response could be viewed as a series of three overlapping successive phases with increasingly complex trophic functional systems for using oxygen since it evolves from ischemia to neovascularization\textsuperscript{[15,17]}.

The first or immediate phase has been referred to as the nervous phase because sensory (stress, inflammatory, pain and analgesia) and motor (contraction and relaxation) alterations, including vasomotor changes, respond
Interstitial infiltration by platelets and leukocytes, all of which release pro-inflammatory cytokines as well as substrates including glucose, amino acids and lipids. In addition, the lymphatic circulation (L) is activated. A: Arterial microcirculation; V: Post-capillary venous circulation.

Figure 2  First or immediate phase of the acute inflammatory response. On the left side, a schematic representation in which the tissue suffers the injury and therefore necrosis of the epithelial cells are produced. In turn, on the right side, the beginning of the tissue inflammatory response in response to necrosis is shown. This initial phase presents ischemia-reoxygenation and interstitial edema (E) with interstitial infiltration of mediators of the stress response as well as substrates including glucose, amino acids and lipids. In addition, the lymphatic circulation (L) is activated, A: Arterial microcirculation; V: Post-capillary venous circulation.

Accumulating evidence demonstrates that platelets contribute to the initiation and propagation of the inflammatory process. These cells are relecet with secretory granules, α-granules, dense granules and lysosomes. Platelet α-granules influence inflammation both by expressing receptors that facilitate adhesion of platelets to other vascular cells (e.g., P-selectin) and by releasing a wide range of chemokines, among which CXCL4 and CLXL7 are the most abundant. Also, platelet α-granules contain a variety of both pro- and anti-angiogenic proteins. Growth factors stored in α-granules include vascular endothelium growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF). Platelet dense granules, on the other hand, contain high concentrations of low molecular weight compounds that potentiate platelet activation (e.g., Adenosine diphosphate, serotonin and calcium) (Figure 3).

In the post-traumatic local inflammatory response, the activation of the innate immune system is not only based on the recognition of danger signals or danger-associated molecular patterns (DAMPs), but also relies on the presence of pathogen-associated molecular patterns (PAMPs). DAMPs and PAMPs are recognized by pattern-recognition receptors (PRRs) that are either cytoplasmic, membrane-bound or secreted. The most intensely studied PRRs are the Toll-like receptors (TLRs), in addition to innate immune receptors, the nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) (Figure 3). All these receptors activate signaling cascades depending on the presence of pathogen-associated molecular patterns (PAMPs).

In the acute inflammatory response, the activation of toll-like receptors (TLRs) results in the expression of pro-inflammatory cytokines and chemokines, which recruit and activate leukocytes and other immune cells. These cells then release additional pro-inflammatory cytokines and chemokines, which further activate the innate immune system. This process is known as the amplification loop and is crucial for the effective response against pathogens.

Figure 3  Immune or intermediate phase of the post-traumatic acute inflammatory response. Interstitial infiltration by platelets and leukocytes, all of them entrapped in the provisional extracellular matrix (left). Underlying the wound crust (Cr) that is formed later, the leukocytes change their phenotype to promote the resolution of the inflammatory response and wound repair by re-epithelialization and scar formation (right). C: Coagulation with fibrin-platelet clot. A: Arterial microcirculation; V: Post-capillary venous circulation; L: Lymphatic circulation.
Angiogenesis is based on endothelial sprouting or intussusceptive (non sprouting) microvascular growth[31]. However, angiogenesis can also result from the recruitment of several cell populations or selected subpopulations of bone marrow-derived endothelial progenitor cells[32]. Angiogenesis is regulated by numerous “classical” factors, including VEGF, FGF-2, transforming growth factor (TGFs) angiopoietins, PDGF, thrombospondin-1 and angiotatin. Non-classic endogenous stimulators of angiogenesis include erythropoietin, angiotensin II, endothelins, adrenomedulin, adipokines, neuropeptide-Y, vasooactive intestinal peptide and substance P[33]. VEGF and FGF-2 occupy the center stage in the angiogenesis field. They act in synergy to stimulate endothelial cell function during angiogenesis in tissue repair[34]. In this last phase, the endocrine phenotype favors nutrition mediated by the blood capillaries. Through initial and excessive proliferation, the endothelial cells could play a key role in the previous phase as antioxidant and anti-enzymatic cells, including induction of the acute phase response, considered the humoral arm of innate immunity[15, 36]. Angiogenesis is closely associated with granulation tissue formation and remodeling. As granulation tissue forms in the healing wound, the vascular cells intermingle with the provisional matrix, which is composed mainly of fibrin, fibronectin and vitronectin[35]. Then, the new blood vessels associated with fibroblasts and macrophages replace the fibrin matrix with granulation tissue, forming a new substrate for keratinocyte migration[36] (Figure 1).

The resolution of the inflammatory response is mainly mediated by families of local-activity mediators that are biosynthesized from the essential fatty acids eicosapentaenoic acid and docosahexaenoic acid. These resolution mediators are termed resolvins, maresins and protectins[37]. Inflammation resolution is also mediated by lipoxins that are generated through platelet-leukocyte interactions[38] (Figure 3). It has been also proposed that regulatory T cells (Treg cells) have evolved to provide a tissue-protecting mechanism driven by low oxygen tension, i.e., hypoxia, in the inflamed tissues. The hypoxia-adenosinergic pathways might govern the production of immunosuppressive molecules that have already been implicated in the activities of Treg cells[39]. In this way, Treg cells could exert their suppressive function with local downregulation of immune response, inducing “immunnodormancy” and protecting tissues from collateral tissue damage, thus improving healing[37]. The progressive resolution of inflammation favors wound re-epithelization. Fibroblasts can also contribute to the resolution of inflammation by withdrawing survival signals and normalizing chemokine gradients, thereby allowing infiltrating leukocytes to undergo apoptosis or leave the tissues through the draining lymphatics[38]. Remodeling begins two to three weeks after injury and lasts for a year or more. Most of the endothelial cells, macrophages and myofibroblasts, undergo apoptosis, leaving a mass that contains few cells and consists mostly of collagen and other extracellular matrix proteins[35]. However, the prognosis of extensive and deep wounds is not entirely satisfactory because of complex, which leads to IKB protein ubiquitylation and subsequent degradation. This results in the release of cytoplasmic NF-κB complexes, which then translocate to the nucleus and drive the expression of target genes[29]. Thus, the expression of inducible genes leading to the synthesis of cytokine receptors, adhesion molecules and autacoids in the traumatized tissue is induced[29].

Leukocytes transverse the subendothelial basement membrane during their immunological surveillance patrol through tissues. This process, called diapedesis, is strongly enhanced under the influence of inflammation. The preferred extravasation sites of leukocytes are the venules[26]. Immediately after injury, extravasated neutrophils are entrapped in the fibrin-platelet clot. In the interstitium, the recruited and activated neutrophils begin the debridement of devitalized tissue and attack infectious agents. To perform this task, they release a large variety of active antimicrobial substances (ROS, cationic peptides, eicosanoids) and proteases (elastase, cathepsin G, proteinase 3 and urokinase-type plasminogen activator)[27]. Neutrophils also store pentraxins 3 and release it in response to inflammatory signals because it is an acute phase reactant[29] (Figure 3).

As monocyes extravasate from the blood vessel they become activated and differentiate into mature tissue macrophages. This transformation implies major changes in gene expression and cell function. The differential activation of macrophages is involved in many facets of tissue injury and inflammation. M1 macrophages express pro-inflammatory cytokines, such as IL-1, IL-6, IL-23 and interferon (IFN)-γ, as well as reactive oxygen and nitrogen species, which are involved in phagocytosis and the killing of microbes. They also promote type 1 immune responses[27]. M2 or alternatively activated macrophages fail to express pro-inflammatory mediators and are involved in angiogenesis, tissue remodeling and the resolution of inflammation. Therefore, they are supposed to promote repair functions[12, 27]. T-helper cells play critical roles in modulating the differential activation of type 2 macrophages. T-helper (Th1) cells produce pro-inflammatory cytokines, i.e., IFN-γ and TNF-α, which skew macrophages into the M1 phenotype. In contrast, type 2 T-helper (Th2) cells produce IL-4, IL-5, IL-13 and IL-10, which are responsible for inducing the alternatively activated macrophages or M2 macrophages[29]. Finally, it has been speculated that metabolic changes in the local milieu may program dendritic cells and other innate cells at the site of inflammation to induce a heterogeneous Th2 response[28]. Although neutrophils, macrophages and T lymphocytes are considered central in the pathogenesis of post-traumatic inflammation, recent studies also imply the involvement of mast cells and B lymphocytes as modulators of the inflammatory response and wound healing[13, 29].

In the final and lasting phase of the wound healing reaction, the angiogenic phenotype is predominant because angiogenesis permits numerous substances, including hormones, to be transported by the blood circulation. Angiogenesis is based on endothelial sprouting or intussusceptive (non sprouting) microvascular growth[31]. However, angiogenesis can also result from the recruitment of several cell populations or selected subpopulations of bone marrow-derived endothelial progenitor cells[32]. Angiogenesis is regulated by numerous “classical” factors, including VEGF, FGF-2, transforming growth factor (TGFs) angiopoietins, PDGF, thrombospondin-1 and angiotatin. Non-classic endogenous stimulators of angiogenesis include erythropoietin, angiotensin II, endothelins, adrenomedulin, adipokines, neuropeptide-Y, vasooactive intestinal peptide and substance P[33]. VEGF and FGF-2 occupy the center stage in the angiogenesis field. They act in synergy to stimulate endothelial cell function during angiogenesis in tissue repair[34]. In this last phase, the endocrine phenotype favors nutrition mediated by the blood capillaries. Through initial and excessive proliferation, the endothelial cells could play a key role in the previous phase as antioxidant and anti-enzymatic cells, including induction of the acute phase response, considered the humoral arm of innate immunity[15, 36]. Angiogenesis is closely associated with granulation tissue formation and remodeling. As granulation tissue forms in the healing wound, the vascular cells intermingle with the provisional matrix, which is composed mainly of fibrin, fibronectin and vitronectin[35]. Then, the new blood vessels associated with fibroblasts and macrophages replace the fibrin matrix with granulation tissue, forming a new substrate for keratinocyte migration[36] (Figure 1).

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scar formation and loss of normal function and skin appendages. Therefore, reducing the formation of scars and re-establishing the normal anatomy and function of the skin and its appendages have become the aim of regenerative medical research.

**WOUND HEALING REPAIR USING EMBRYONIC MECHANISMS**

Inflammation, whether acute or chronic, produces tissue remodeling. In this way, it has been proposed that the inflammatory response has features in common with tissue development, which requires involution of pre-existing tissue elements. The ability of the tissues to involute or dedifferentiate could represent a return to early stages of development. Particularly, involution or dedifferentiation could form an effective defense mechanism to escape death after injury. Thus, this mechanism could make retracing an ancient, efficient and well-known route possible for repairing the injured tissue, just like the initial phases of embryonic development. The correlation that can be established between the embryonic and the inflammatory events suggests that the results obtained from research into both great fields of knowledge would favor each other and promote their development.

In the adult body, many pathways that play an essential role during embryological development are inactivated later in life, although some of them may be transiently expressed during the adult repair process. This ability of the tissues to involute or dedifferentiate could constitute an effective solution against any type of injury. Through dedifferentiation, tissues have the chance to reform and remodel themselves according to the new environmental situation imposed on them.

The fetus is uniquely capable of healing skin wounds without scar formation and provides a model of ideal tissue repair. Understanding the biology of this process may allow us to modulate wound healing in children and adults to become more fetal-like. Tissue repair in the embryo and to a certain extent in adults too, appears to recapitulate those cell machineries used by embryos to undergo the natural tissue movements of morphogenesis, such as gastrulation and neural tube closure. One key difference between embryonic and adult repair, which may explain why one heals perfectly and the other scars, is the presence of an inflammatory response at sites of adult repair while there is none in the embryo. However, total knockdown of inflammation is clearly not going to be an optimal treatment for post-natal scarring.

The infiltration of platelets, mast cells, neutrophils and macrophages which characterizes the early postnatal wound is greatly diminished in fetal wounds. However, fetal wound healing is additionally characterized by a distinct extracellular matrix, anti-inflammatory and growth factor profile and a more important role for stem cells. If so, we could hypothesize that to promote adult wound repair by regeneration, current therapies need to be attempted to recapitulate singular aspects of the fetal regenerative phenotype. The evidence suggests that there may be an early critical window in postnatal wound healing that may be amenable to manipulation so as to provide a permissive environment for scarless wound healing to proceed.

In this way, the early post-traumatic inflammatory response could recapitulate ontogeny by re-expressing two hypothetical extra-embryonic trophic axes, that is amniotic and yolk sac or vitelline in the interstitial space of the injured tissue. Likewise, the body could be repaired according to embryonic biochemical patterns through the expression of extra-embryonic functions. If so, the early inflammatory steps could represent the postnatal debut of ancestral biochemical mechanisms that were used for normal embryonic development. The re-expression of these ancient mechanisms is perhaps hard to recognize because they are anachronistic during postnatal life and are established in a different environmental medium.

After fertilization, the first stage of embryogenesis is the zygote, which undergoes cleavage by mitosis. When the morula stage is reached, the embryo establishes polarity. The cells bind tightly to each other, forming a compact sphere with two cell layers. The outer most layer becomes the trophoblast, giving rise to the placenta, and the inner cells become the inner cell mass, giving rise to the embryo and the remaining structures, including the amnion, yolk sac and allantois. The molecular and cellular contributions of the extra-embryonic tissues surrounding the fetus, namely the exocoelomic cavity, the amnion, the trophoblast and the yolk sac, to the interstitial space located between them, the mesoderm, are essential for organogenesis. In fact, the intraembryonic mesoderm generated during gastrulation may represent the internalization of the functions that charac-
During trophoblast differentiation, trophoblastic cells regulate the lipid metabolism and favor phagocytosis. Under stress, activated the complement-coagulation system, phenotype reduces oxidative, nitrosative and enzymatic and release of acute phase proteins, this extra-embryonic nutrition (carbohydrate, protein and lipid accumulation for embryo layer is the source of several proteins including acute endocytosis/digestion dermal layers have absorptive functions and are active in facing the yolk sac cavity blood islands that promote the development of hema external mesothelial layer, a vascular mesenchyme, with an endodermal layer facing the yolk sac cavity. The mesothelial and endodermal layers have absorptive functions and are active in endocytosis/digestion. In addition, the endodermal layer is the source of several proteins including acute phase proteins. A major function of the yolk sac is carbohydrate, protein and lipid accumulation for embryo nutrition (vitellum). In addition, through the synthesis and release of acute phase proteins, this extra-embryonic phenotype reduces oxidative, nitrosative and enzymatic stress, activates the complement-coagulation system, regulates the lipid metabolism and favors phagocytosis. During trophoblast differentiation, trophoblastic cells also exhibit intense phagocytic activity leading to events as diverse as engulfment and destruction of extracellular material and the production of inflammatory mediators that may modulate both the immune and trophoblast invasiveness (Figure 4).

The molecular and cellular contribution made by the above-mentioned extra-embryonic membranes, i.e., exocoelomic cavity, amnion, yolk sac and trophoblast to the intra-embryonic mesoderm, could be essential for embryo development and organogenesis. Moreover, these primitive extra-embryonic structures can be internalized by the embryo at early development stages. Consequently, the hypothesized re-expression of these extra-embryonic functions after injury during postnatal life could be a key process needed to repair the injured organism. If so, the recapitulation of extra-embryonic functions through the organism could be internalized into the injured interstitium, thus inducing a process similar to the early embryonic process for tissue repair by regeneration and/or fibrosis.

**INFLAMMATORY ENDOTHELIAL EGG**

It could be proposed that recapitulation of extra-embryonic functions during wound repair is made up through the activation of two functional axes, namely: the coelomic-amniotic axis and the trophoblastic-vitelline axis. Both axes would polarize in the interstitium of the wounded tissue, thus promoting the development of a new tissue (Figure 4).

In surgical-related inflammation, the interstitium is surrounded by an inflamed heterogeneous endothelium. Thus, this inflammatory endothelium would get cellular and molecular mediators through the post-capillary venule endothelium, the high endothelial venule endothelium in the lymph nodes and, to a lesser degree, through the capillary endothelium. Ultimately, the lymphatic endothelium has a basic excretory function. The complex made up by this inflamed heterogeneous endothelium and the interstitial space of the injured tissue surrounded by it

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**Table 1 Upregulation of extraembryonic phenotypes that could be involved in the different types of the wound healing reaction**

| Phenotypes                  | Embryonic functions       | Phases of the inflammatory response | Phases of the wound healing reaction |
|-----------------------------|---------------------------|-------------------------------------|--------------------------------------|
| Extraembryonic phenotypes   | Coelomic-amniotic axis    | Nervous phase                        | Stress response - Biogenic amines release |
|                             |                           | Neurogenic systemic response         | Sensitive and motor alterations       |
|                             | Trophoblastic-vitelline   | Immune phase                         | Ischemia-reperfusion - Local oxidative and nitrosative stress |
|                             | axis                      | Bone-marrow related response         | Hydroelectrolytic alterations - Edema |
| Embryonic phenotypes        | Gastrulation              | Angiogenic phase                     | Inflammation blood cells - Coagulation |
|                             |                           | Remodeling response                  | Enzymatic stress                     |
|                             |                           |                                     | Corticosuprarenal hormones - Local storage |
|                             |                           |                                     | Hematopoietic stem cells             |
|                             |                           |                                     | Mesenchymal stem cells               |
|                             |                           |                                     | Endothelial progenitor cells         |
|                             |                           |                                     | Myofibroblasts                       |
|                             |                           |                                     | Angiogenesis                         |
|                             |                           |                                     | Endothelial egg                      |
|                             |                           |                                     | Re-epithelization                    |
|                             |                           |                                     | Fibrosis                             |
has been compared with an “endothelial egg” (Figures 5 and 6). Thus, in the interior of this heterogeneous endothelial sheath, the successive evolutive phases of wound repair with interstitial edema, activation of the lymphatic circulation and a hypoxic environment that could be an ideal stem cell niche, can be represented. Then, hemostasis by the formation of a platelet-fibrin clot occurs. After that, neutrophils, monocytes and lymphocytes are recruited and finally, new tissue is formed by regeneration, i.e., keratinocytes and granulation tissue, i.e., fibroblasts and endothelial cells, which form a substrate to complete the wound repair by fibrosis (Figures 6 and 7).

However, cutaneous wound healing is not only a local process, but also a complex process involving systemic inflammatory alterations related to the stress response (Figures 5 and 6). The magnitude of this systemic response may reflect the demands of the “endothelial egg” required for wound repair (Figure 7). In this sense, we have been trying to establish similarities between the complex pathophysiological mechanisms developed in wound healing and the pluripotential extra-embryonic pathways during embryonic development (Figures 6 and 7).

The pathological neuromuscular response secondary to a wound induces sensory changes (stress, inflammatory pain, analgesia) and motor alterations (fight-to-flight and withdrawal reflexes, tachycardia and vasoconstriction-vasodilation). This upregulated extra-embryonic phenotype would induce a sudden and early neurogenic response with systemic cardiovascular, hemodynamic and hydro-electrolytic alterations (Figures 6 and 7). Systemic and local ischemia-reperfusion produce sudden hydroelectrolytic changes associated with abnormal ion transport. In this early response, cells that produce substances for export first

**RECAPITULATED COELOMIC-AMNIOTIC FUNCTIONS: A NEUROGENIC SYSTEMIC RESPONSE**

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The inflammatory bone marrow-related response induced by wounds could be considered both a key and complementary arm of the systemic response to injury. The inflammatory activation of the bone marrow stem cell niche indicates the stimulation of hematopoietic stem cells and mesenchymal stem cells, both which are multipotent stem cells. Hematopoietic stem cells are the progenitors of all blood and immune cells. Macrophages generated from hematopoietic stem cells are the dominant phagocytes at wound-healing sites. Profibrotic macrophages, in particular, are intimately involved in wound healing through the production of mediators that directly activate fibroblasts, including transforming growth factor-beta (TGF-β), PDGF and IGF-1. Nevertheless, although macrophages are required for the initiation and maintenance of fibrosis, they are also involved in its suppression, resolution and reversal. Therefore, macrophage activation is best considered as a continuous spectrum of phenotypic characteristics. In this context, circulating endothelial cells have also proved to be an important marker of vascular remodeling associated with wound healing. Angiogenesis is needed during embryonic development and plays important roles in wound healing and tissue ischemia throughout postnatal life. Although the major physiological role of circulating endothelial progenitor cells is to maintain vascular integrity, they can also participate in revascularization of ischemic wounds.

Furthermore, the upregulated trophoblastic-vitelline phenotype could mediate the inflammatory response through a lipid metabolic switch linked to steroid and acute phase response protein synthesis, respectively. This slower response would therefore be developed by steroidogenic cells that store very little steroid hormones, in which case a rapid steroidogenic response would require immediate synthesis of new steroids, such as cortisol. The increase of the acute phase protein synthesis, i.e., innate immunity, by the gut-liver axis is linked with the acute phase response and follows the upregulation of pro-inflammatory cytokines and chemokines.

COUPLING THE RECAPITULATED EXTRA-EMBRYONIC AXES IN THE “INFLAMMATORY ENDOTHELIAL EGG”

The systemic recapitulated extra-embryonic axes, i.e., coelomic-amniotic and trophoblastic-vitelline, are focused and coupled in the endothelial inflammatory egg. This interstitial integration of both pathological axes, i.e., neurogenic and bone-marrow-related in the wounded tissue, could finally induce a gastrulation-like process (Figures 6 and 7). Gastrulation, which involves the “de novo” formation of reparative tissue, is based on the recapitulation of the intra-embryonic mesenchyme formation process. In essence, the integration of both extraembryonic-related phenotypes coelomic-amniotic and trophoblastic-vitelline by the multipotent mesenchymal stem/stromal cells would support the functional and metabolic heterogeneity needed for successively modulating their injured microenvironment during embryonic development. Therefore, the interaction of extraembryonic functional axes recapitulated after injury in the interstitium of the damaged tissue allows for the recapitulation of the mechanisms characteristic of gastrulation, subsequently forming a mesenchyme in the endothelial inflammatory egg similar to that present in the early development phases.

Therefore, the early post-injury induction of extraembryonic mechanisms that favors the beginning of the repair process is undermined throughout the evolution of the wound healing reaction. In this way, the tissue that initiates its development inside the hypothesized endothelial-
fetal egg seems to suffer an immunological injury from the host organism. This reaction, similar to what takes place in organ transplantation, i.e., host-versus-graft reaction, would explain the involution of the newly formed tissue until constructing, in the long term, the devitalized scar tissue. The study of those factors that induce this switch in the host organism, by which it gives up its gestating role and adopts a rejection attitude against already newly formed tissue, would explain why some authors consider that, in order to achieve tissue repair, inflammation is not needed\(^\text{11}\).

**CONCLUSION**

In the current review, the wound healing reaction is considered a systemic inflammatory response made up by upregulated extra-embryonic functions, i.e., coelomic-amniotic and trophoblastic-vitelline. The confluence and overlapping of these functions produce an injured tissue that would adopt an egg-like configuration that is one mainly made up of two structures: a round interstitial space surrounded by a heterogeneous endothelium. Therefore, cellular and molecular mediators from the extra-embryonic functions recapitulated by the injured organisms would induce a gastrulation-like process in this inflammatory endothelial egg from which tissue repair is produced either by regeneration and/or fibrosis.

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