MINIREVIEWS

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 universality 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.

Core tip: In this review, we propose an integrative molecular point of view about wound healing. Wound healing could be associated with the upregulation of functions characteristic of embryonic development. The repair of adult tissues using upregulated embryonic mechanisms could explain the ubiquity of the inflammatory response against injury, regardless of its etiology.

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INTRODUCTION

Wound tissue repair can be realized by regeneration and/or fibrosis. While regeneration describes the specific substitution of the injured tissue, tissue fibrosis displays an unspecific form of healing in which the wounded tissue heals by scar formation[1,2]. Since repair by fibrosis can be considered an unsuccessful attempt of wound tissue repair by regeneration, the fibrotic process supposedly represents an insufficient repair method and, therefore, a pathological response. This is the reason why the inflammatory response associated with scar formation is also commonly labeled pathological. In this way, regenerative healing has a notable absence of inflammatory cell activity[3-5]. Consequently, inflammatory response mediators have been a focus of investigation in studies aiming to curtail scarring[5,6].

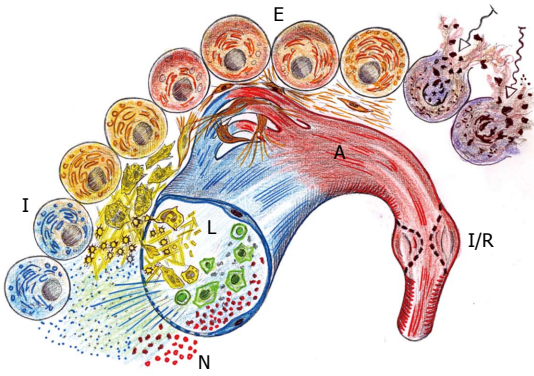The standard view of inflammation as a reaction to injury or infection might need to be expanded to account

Figure 1 Schematic representation of the different stages of wound repair. During the post-traumatic local inflammatory response three successive and overlapped phases: in the arterial side of the microcirculation (red), a nervous (N) or immediate phase with ischemia-reperfusion (I/R) occurs; in the post-capillary venule (blue), an immune (I) or intermediate phase with a leukocytic (L) phenotype is expressed; and, finally an endocrine (E) or late with an angiogenic (A) phenotype is developed, which implies the capillaries neoformation.

for the inflammatory processes induced by other types of adverse conditions[7]. 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[7]. However, human aging can be explained by the emerging concept of inflamm-ageing, *i.e.*, - a combination of inflammation and aging[8]. Inflamm-ageing seems to favor the onset of typical age-related diseases like atherosclerosis, dementia, osteoporosis and cancer[9]. Inflammatory mechanisms are also involved in physiological processes, like physical exercise, embryonic development and gestation, and indeed there is the hypotheses that the evolution of the living species could be based on inflammatory remodeling of organisms induced by environmental factors[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[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[4,12]. 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[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[14].

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[15]. Likewise, inflammation could facilitate the integration of the pathophysiological mechanisms involved in the different phases of wound repair by scar formation[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[15,16] (Figure 1).

In turn, we have suggested that these phenotypes could represent the expression of trophic functional systems of increasing metabolic complexity[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[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[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[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
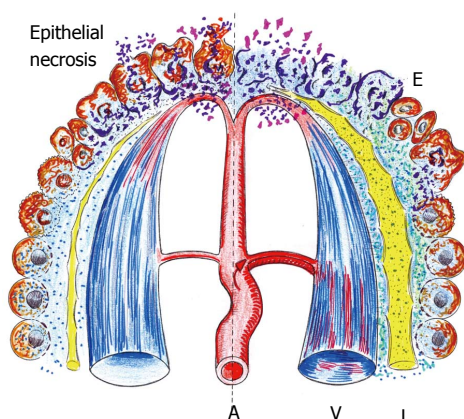
Figure 2 First or immediate phase of the acute inflammatory response. On the left side, a schematic representation in which the tissue suffers the injury and therefore necrosis of the epithelial cells are produced. In turn, on the right side, the beginning of the tissue inflammatory response in response 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.
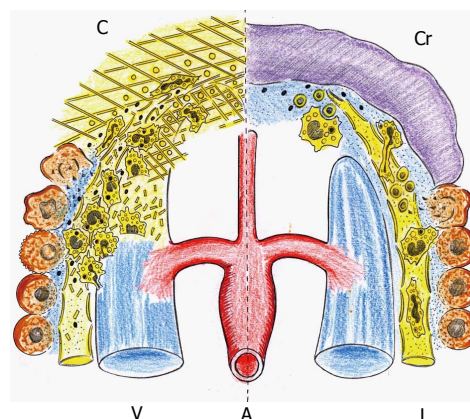

Figure 3 Immune or intermediate phase of the post-traumatic acute inflammatory response. Interstitial infiltration by platelets and leukocytes, all of them entrapped in the provisional extracellular matrix (left). Underlying the wound crust (Cr) that is formed later, the leukocytes change their phenotype to promote the resolution of the inflammatory response and wound repair by re-epithelization and scar formation (right). C: Coagulation with fibrin-platelet clot. A: Arterial microcirculation; V: Post-capillary venous circulation; L: Lymphatic circulation.

to the injury. This early pathological activity of the body's nociceptor pathways is associated with stress through the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary axes, the sympathetic nervous system and the renin-angiotensin-aldosterone system. This initial phase presents ischemia-reoxygenation, oxidative and nitrosative stress, and interstitial edema with selective interstitial infiltration by mediators of the stress response, such as catecholamines, adrenocorticotrophic hormone, glucocorticoids and angiotensin, as well as glucose, amino acids and lipids, all of them derived from earlier metabolic alterations, including hyperglycemia, protein catabolism and lipolysis. In addition, interstitial edema favors nutrition by diffusion through the injured tissue and activation of the lymphatic circulation (circulatory switch)[2,15,17] (Figure 2).

In the succeeding immune or intermediate phase of the acute inflammatory response, the wounded tissue that has previously suffered ischemia-reperfusion is infiltrated by inflammatory cells and sometimes by bacteria. This phase presents enzymatic stress with migration of macrophages and dendritic cells to lymph nodes, where they activate T and B cells, *i.e.*, innate and adaptive immune response. Interstitial invasion by leukocytes would create a new trophic axis.

Accumulating evidence demonstrates that platelets contribute to the initiation and propagation of the inflammatory process. These cells are replete 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 vascu-

lar endothelium growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), hepatocyte growth factor 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)[18,19] (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)[20]. 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)[21]. In particular, NLRs form central molecular platforms that organize signaling complexes, such as inflammasomes and NOD signalosomes. The term inflammasome was coined to describe the high molecular weight complex that activates inflammatory caspases and cytokine interleukin-1 (IL-1)β[22]. All these receptors activate signaling cascades that is based on enzymatic intra- and extra-cellular digestion[15,17] and lead to activation of mitogen activated protein kinases and nuclear factor kappa B (NF-κB)[21,22]. Once activated, TLRs induce different signaling cascades depending on the adaptor protein, ultimately leading to the activation of the transcription factors NF-κB, AP-1 and interferon-regulatory factor[22]. The regulatory event of NF-κB activation is the phosphorylation of inhibitor of kappa B kinase complex (IKB) proteins by the IKB kinase

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[23]. Thus, the expression of inducible genes leading to the synthesis of cytokine receptors, adhesion molecules and autacoids in the traumatized tissue is induced[24].

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[25]. 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)[12]. Neutrophils also store pentraxins 3 and release it in response to inflammatory signals because it is an acute phase reactant[26] (Figure 3).

As monocytes 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 I 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[28]. 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[29]. 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[12,30].

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 intus-

susceptive (nonsprouting) 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 "*classic*" factors, including VEGF, FGF-2, transforming growth factor (TGFs) angiopoietins, PDGF, thrombospondin-1 and angiostatin. Non-classic endogenous stimulators of angiogenesis include erythropoietin, angiotensin Ⅱ, endothelins, adrenomedulin, adipokines, neuropeptide-Y, vasoactive intestinal peptide and substance P[31]. 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[33]. 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[15,16]. 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[33]. Then, the new blood vessels associated with fibroblasts and macrophages replace the fibrin matrix with granulation tissue, forming a new substrate for keratinocyte migration[34] (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[35]. Inflammation resolution is also mediated by lipoxins that are generated through platelet-leukocyte interactions[36] (Figure 3). It has been also proposed that regulatory T cells (Treg cells) have evolved to provide a complementary immunological arm to a physiological 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[37]. In this way, Treg cells could exert their suppressive function with local downregulation of immune response, inducing "*immunodormancy*" 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[34]. However, the prognosis of extensive and deep wounds is not entirely satisfactory because of
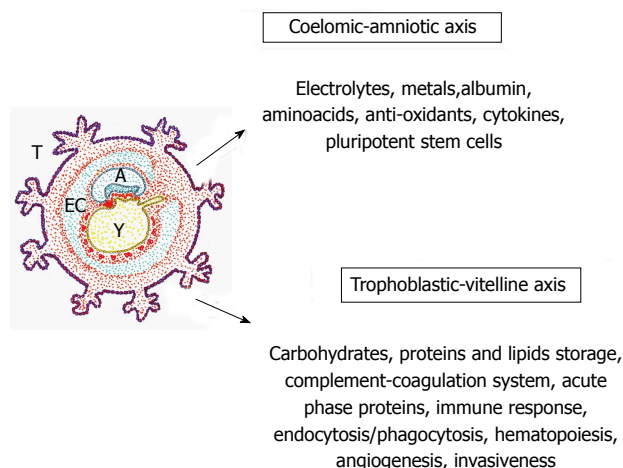
Coelomic-amniotic axis

Electrolytes, metals,albumin, aminoacids, anti-oxidants, cytokines, pluripotent stem cells

Trophoblastic-vitelline axis

Carbohydrates, proteins and lipids storage, complement-coagulation system, acute phase proteins, immune response, endocytosis/phagocytosis, hematopoiesis, angiogenesis, invasiveness

Figure 4 Hypothesized functions by ontogenic recapitulation in the traumatized tissue. These functions could be similar to the extra-embryonic coelomic-amniotic and trophoblastic-vitelline functions during early embryonic development. The extra-embryonic coelom or exocoelomic cavity surrounds the blastocyst, which is composed of the amnion and the primary yolk sac. EC: Exocoelomic cavity; A: Amnion; T: Trophoblast; Y: Yolk sac or vitellum.

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[39,40].

WOUND HEALING REPAIR USING EMBRYONIC MECHANISMS

Inflammation, whether acute or chronic, produces tissue remodeling[9]. 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[15,16]. The ability of the tissues to involute or dedifferentiate could represent a return to early stages of development[41]. 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[2,41]. 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[41].

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[41,42]. 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[10].

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[43-45]. 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[41,46]. 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[46]. The infiltration of platelets, mast cells, neutrophils and macrophages which characterizes the early postnatal wound is greatly diminished in fetal wounds[43,47]. 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[5,6]. 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[5]. 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[5].

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[41] (Figure 4). 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[41,48] (Table 1).

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 allantoids[49] (Figure 4). 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 intra-embryonic mesoderm generated during gastrulation may represent the internalization of the functions that charac-

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	Neurogenic systemic response	Stress response - Biogenic amines release
				Sensitive and motor alterations
				Ischemia-reperfusion - Local oxidative and nitrosative stress
				Hydroelectrolytic alterations - Edema
				Inflammation blood cells - Coagulation
	Trophoblastic-vitelline axis	Immune phase	Bone-marrow related response	Enzymatic stress
				Corticosuprarenal hormones - Local storage
				Hematopoietic stem cells
				Mesenchymal stem cells
				Endothelial progenitor cells
Embryonic phenotypes	Gastrulation	Angiogenic phase	Remodeling response	Myofibroblasts
				Angiogenesis
				Endothelial egg
				Re-epithelization
				Fibrosis

terize these extra-embryonic functions[50].

The hypothetical recapitulation of these initial phases of the embryonic development during the early surgical inflammatory response would imply the expression of functions similar to the extra-embryonic structures. Accordingly, the phenotype that could be adopted by the inflamed interstitium may induce the accumulation of fluid with similar characteristics to coelomic fluid. In essence, interstitial edema with high levels of proteins, in particular albumin, as well as electrolytes, metals, amino acids, antioxidants, cytokines and cholesterol-derived hormone, would be produced in the inflammatory exudates[51,52]. Amnion-derived multipotent progenitor cells also secrete a unique combination of cytokines and growth factors called the "*amnion-derived cellular cytokine solution*" which establishes a connection between mesenchymal and epithelial cells during embryo development[53]. In this sense, the amniotic fluid surrounding the fetus may therefore be an extension of the extracellular space of the fetal tissues[54]. The amniotic-like phenotype could also offer the stem cell a hypoxic and hydrated interstitial axis with cytokines and growth factors, favoring not only nutrition by diffusion, but also transport, excretion and bacteriostatic and anti-inflammatory protection[54,55] (Figure 4).

The wall of the secondary yolk sac is formed by an external mesothelial layer, a vascular mesenchyme, with blood islands that promote the development of hematopoiesis and angiogenesis[56] and an endodermal layer facing the yolk sac cavity[53]. The mesothelial and endodermal layers have absorptive functions and are active in endocytosis/digestion[56,57]. In addition, the endodermal layer is the source of several proteins including acute phase proteins[58]. A major function of the yolk sac is carbohydrate, protein and lipid accumulation for embryo nutrition (*vitellum*)[57]. 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[59]. 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[60,61] (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[50]. 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[2,41]. 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
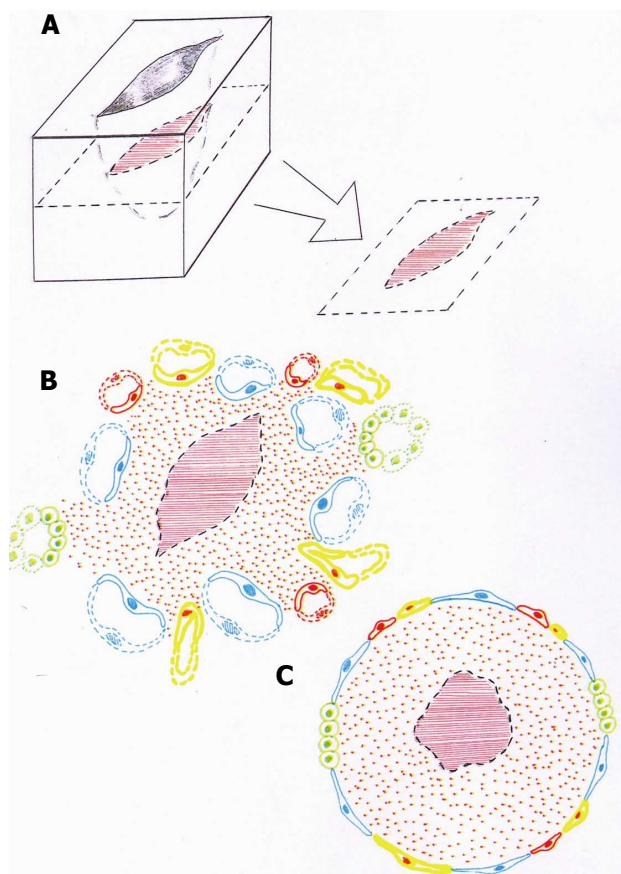
Figure 5 Figurative representation of a skin wound. The wound (A) is surrounded by different types of inflammatory venous, arterial and lymphatic endothelia (B). This heterogeneous inflammatory endothelium could be represented like a sheath of the inflamed interstitium that surrounds in turn the wound or broken tissue (C).

Figure 6 Schematic representations of the heterogeneous endothelium that surrounds the wounded tissue. A: The endothelium that cover the wound (W) and the damaged interstitium (it) are made up by the post-capillary venous endothelium (pcve), the high endothelial venular endothelium (heve), the lymphatic endothelium (le) and the blood capillary endothelium (bce); B: The inflammatory response is produced into the injured interstitium. The inflammatory mediators, molecules and cells, invade this interstitial space crossing through a sheath of heterogeneous endothelia.

has been compared with an "*endothelial egg*"[62] (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[12,14,30,34] (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[2,62]. 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[2,10,41,62]. In this way, the recapitulation of coelomic-amniotic and trophoblast-vitelline functions is selectively integrated into the injured area. The reca-
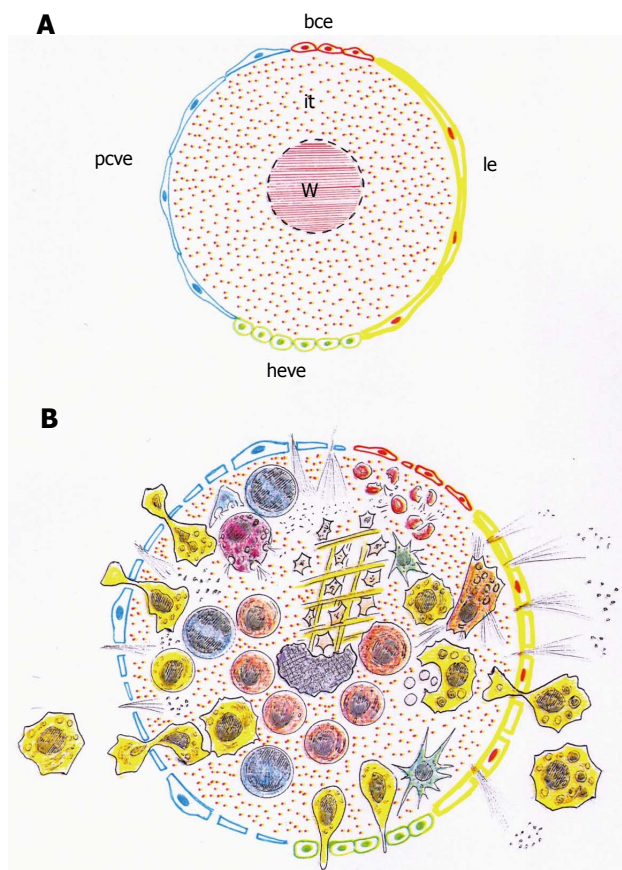
pitulation of the extra-embryonic coelomic and amniotic functions could be represented by initially activating the systemic neurogenic axis, while the latter recapitulation of the trophoblast and yolk sac functions would be carried out by activating the systemic bone-marrow axis (Figure 7).

RECAPITULATED COELOMIC-AMNIOTIC FUNCTIONS: A NEUROGENIC SYSTEMIC RESPONSE

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 hydroelectrolytic alterations[2,62]. Systemic and local ischemia-reperfusion produce sudden hydroelectrolytic changes associated with abnormal ion transport[63]. In this early response, cells that produce substances for export first
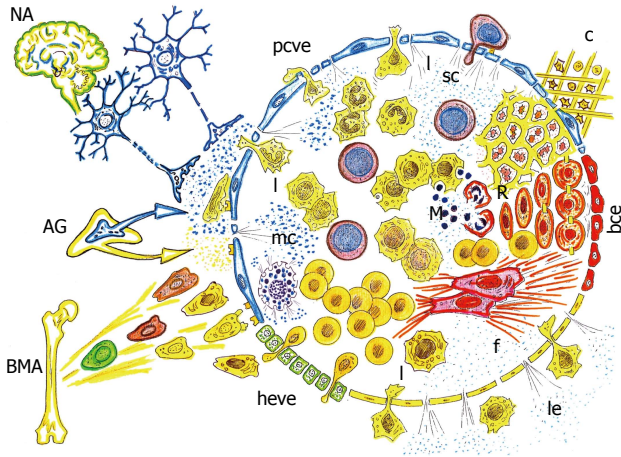
Figure 7 Neurogenic and bone marrow-related axes coupled in the inflamed endothelial egg, after wound. The upregulated extra-embryonic functions, *i.e.*, coelomic-amniotic or neurogenic, and trophoblastic-vitelline or bone marrow-related, are focused in the endothelial inflammatory egg, favoring the induction of a gastrulation-like phenotype, which evolves towards re-epithelization and fibrosis (scar) in post-natal life. NA: Neurogenic axis; AG: Adrenal gland; BMA: Bone marrow-related Axis; c: Coagulation; sc: Stem cell; mc: Mast cell. R: Regeneration; f: Fibrosis; l: Leukocytes; M: Microbiome. ve: Post-capillary venous endothelium; heve: High endothelial venular endothelium; le: Lymphatic endothelium; bce: Blood capillary endotelium; pcve: Psot capillary venous endothelium.

synthesize and then store large amounts of molecules, such as biogenic amines and neuropeptides in secretory vesicles ready for rapid release[64]. In this early neurogenic response, the activation of the hypothalamic-pituitary-adrenocortical, sympathetic-adrenal medullary and renin-angiotensin-aldosterone axes occur, with the release of catecholamines, glucocorticoids and mineralocorticoids. Consequently, selective accumulation of these mediators in the "*endothelial inflammatory egg*" is produced because endothelial permeability is increased, especially in postcapillary venules[2,62] (Figure 7).

RECAPITULATED TROPHOBLASTIC-VITELLINE FUNCTIONS: A BONE-MARROW-RELATED RESPONSE

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[65-67]. 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[28]. Nevertheless, although macrophages are required for the initia-

tion and maintenance of fibrosis, they are also involved in its suppression, resolution and reversal[28,68]. Therefore, macrophage activation is best considered as a continuous spectrum of phenotypic characteristics[69]. 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[62]. Although the major physiological role of circulating endothelial progenitor cells is to maintain vascular integrity, they can also participate in revascularization of ischemic wounded tissues[70].

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[2]. 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[2,41,62].

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[41] (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[41]. In essence, the integration of both extra-mbryonic-related phenotypes coelomic-amniotic and trophoblastic-vitelline by the multipotent mesenchymal stem/stromal cells[67,71,72] would support the functional and metabolic heterogeneity needed for successively modulating their injured microenvironment during embryo development[50]. Therefore, the interaction of extra-embryonic 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[2,62].

Therefore, the early post-injury induction of extra-embryonic mechanisms that favors the beginning of the repair process[1] is undermined throughout the evolution of the wound healing reaction. In this way, the tissue that initiates its development inside the hypothesized endothe-

lial 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[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.

REFERENCES

1   **Reinke JM**, Sorg H. Wound repair and regeneration. *Eur Surg Res* 2012; **49**: 35-43 [PMID: 22797712 DOI: 10.1159/000339613]

2   **Aller MA**, Blanco-Rivero J, Arias JI, Balfagon G, Arias J. The wound-healing response and upregulated embryonic mechanisms: brothers-in-arms forever. *Exp Dermatol* 2012; **21**: 497-503 [PMID: 22716244 DOI: 10.1111/j.16000625.2012.01525.x]

3   **Günter CI**, Machens HG. New strategies in clinical care of skin wound healing. *Eur Surg Res* 2012; **49**: 16-23 [PMID: 22797612 DOI: 10.1159/000339860]

4   **Profyris C**, Tziotzios C, Do Vale I. Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics Part I. The molecular basis of scar formation. *J Am Acad Dermatol* 2012; **66**: 1-10; quiz 11-12 [PMID: 22177631 DOI: 10.1016/j.jaad.2011.05.055)]

5   **Leung A**, Crombleholme TM, Keswani SG. Fetal wound healing: implications for minimal scar formation. *Curr Opin Pediatr* 2012; **24**: 371-378 [PMID: 22572760 DOI: 10.1097/MOP.0b013e3283535790]

6   **Rolfe KJ**, Grobbelaar AO. A review of fetal scarless healing. *ISRN Dermatol* 2012; **2012**: 698034 [PMID: 22675640 DOI: 10.5402/2012/698034]

7   **Medzhitov R**. Origin and physiological roles of inflammation. *Nature* 2008; **454**: 428-435 [PMID: 18650913 DOI: 10.1038/nature07201]

8   **Franceschi C**, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000; **908**: 244-254 [PMID: 10911963 DOI: 10.1111/j.1749-6632.2000.tb06651.x]

9   **Caruso C**, Lio D, Cavallone L, Franceschi C. Aging, longevity, inflammation, and cancer. *Ann N Y Acad Sci* 2004; **1028**: 1-13 [PMID: 15915584]

10 **Aller MA**, Arias N, Fuentes-Julian S, Blazquez-Martinez A,

Argudo S, Miguel MP, Arias JL, Arias J. Coupling inflammation with evo-devo. *Med Hypotheses* 2012; **78**: 721-731 [PMID: 22405850 DOI: 10.1016/j.mehy.2012.02.018]

11 **Wynn TA**, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat Med* 2012; **18**: 1028-1040 [PMID: 22772564 DOI: 10.1038/nm.2807)]

12 **Eming SA**, Hammerschmidt M, Krieg T, Roers A. Interrelation of immunity and tissue repair or regeneration. *Semin Cell Dev Biol* 2009; **20**: 517-527 [PMID: 19393325 DOI: 10.1016/j.semcdb.2009.04.009]

13 **Stojadinovic A**, Carlson JW, Schultz GS, Davis TA, Elster EA. Topical advances in wound care. *Gynecol Oncol* 2008; **111**: S70-S80 [PMID: 18793796 DOI: 10.1016/j.ygyno.2008.07.042]

14 **Monaco JL**, Lawrence WT. Acute wound healing an overview. *Clin Plast Surg* 2003; **30**: 1-12 [PMID: 12636211]

15 **Aller MA**, Arias JL, Nava MP, Arias J. Posttraumatic inflammation is a complex response based on the pathological expression of the nervous, immune, and endocrine functional systems. *Exp Biol Med* (Maywood) 2004; **229**: 170-181 [PMID: 14734796]

16 **Aller MA**, Arias JL, Sánchez-Patán F, Arias J. The inflammatory response: an efficient way of life. *Med Sci Monit* 2006; **12**: RA225-RA234 [PMID: 17006415]

17 **Aller MA**, Arias JI, Giner M, Losada M, Cruz A, Alonso-Poza A, Arias J. Oxygen-related inflammatory wound phenotypes. In: Middleton JE, Huntington NY. Wound healing: Process, phases and promoting. New York, NY: Nova Science Publishers, 2011: 1-26

18 **Nurden AT**, Nurden P, Sanchez M, Andia I, Anitua E. Platelets and wound healing. *Front Biosci* 2008; **13**: 3532-3548 [PMID: 18508453]

19 **Blair P**, Flaumenhaft R. Platelet alpha-granules: basic biology and clinical correlates. *Blood Rev* 2009; **23**: 177-189 [PMID: 19450911 DOI: 10.1016/j.blre.2009.04.001]

20 **Matzinger P**. The danger model: a renewed sense of self. *Science* 2002; **296**: 301-305 [PMID: 11951032]

21 **Kluwe J**, Mencin A, Schwabe RF. Toll-like receptors, wound healing, and carcinogenesis. *J Mol Med* (Berl) 2009; **87**: 125-138 [PMID: 19089397 DOI: 10.1007/s00109-008-0426-z]

22 **Martinon F**, Mayor A, Tschopp J. The inflammasomes: guardians of the body. *Annu Rev Immunol* 2009; **27**: 229-265 [PMID: 19302040 DOI: 10.1146/annurev.immunol.021908.132715]

23 **Ghosh S**, Hayden MS. New regulators of NF-kappaB in inflammation. *Nat Rev Immunol* 2008; **8**: 837-848 [PMID: 18927578 DOI: 10.1038/nri2423]

24 **Hanada T**, Yoshimura A. Regulation of cytokine signaling and inflammation. *Cytokine Growth Factor Rev* 2002; **13**: 413-421 [PMID: 12220554]

25 **Eble JA**, Niland S. The extracellular matrix of blood vessels. *Curr Pharm Des* 2009; **15**: 1385-1400 [PMID: 19355976 DOI: 10.1074/jbc.M109.002873]

26 **Manfredi AA**, Rovere-Querini P, Bottazzi B, Garlanda C, Mantovani A. Pentraxins, humoral innate immunity and tissue injury. *Curr Opin Immunol* 2008; **20**: 538-544 [PMID: 18579363 DOI: 10.1016/j.coi.2008.05.004]

27 **Glaros T**, Larsen M, Li L. Macrophages and fibroblasts during inflammation, tissue damage and organ injury. *Front Biosci* (Landmark Ed) 2009; **14**: 3988-3993 [PMID: 19273328]

28 **Mosser DM**, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol* 2008; **8**: 958-969 [PMID: 19029990 DOI: 10.1038/nri2448]

29 **Pulendran B**, Artis D. New paradigms in type 2 immunity. *Science* 2012; **337**: 431-435 [PMID: 22837519 DOI: 10.1126/science.1221064]

30 **Eming SA**, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol* 2007; **127**: 514-525 [PMID: 17299434]

31 **Ribatti D**, Conconi MT, Nussdorfer GG. Nonclassic endogenous novel [corrected] regulators of angiogenesis. *Pharmacol*

Rev 2007; **59**: 185-205 [PMID: 17540906]

32   **Garin G**, Mathews M, Berk BC. Tissue-resident bone marrow-derived progenitor cells: key players in hypoxia-induced angiogenesis. *Circ Res* 2005; **97**: 955-957 [PMID: 16284185]

33   **Chan LK**. Current thoughts on angiogenesis. *J Wound Care* 2009; **18**: 12-14, 16 [PMID: 19131912]

34   **Gurtner GC**, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature* 2008; **453**: 314-321 [PMID: 18480812 DOI: 10.1038/nature07039]

35   **Ariel A**, Serhan CN. Resolvins and protectins in the termination program of acute inflammation. *Trends Immunol* 2007; **28**: 176-183 [PMID: 17337246 DOI: 10.1016/j.it.2007.02.007]

36   **Yacoubian S**, Serhan CN. New endogenous anti-inflammatory and proresolving lipid mediators: implications for rheumatic diseases. *Nat Clin Pract Rheumatol* 2007; **3**: 570-579; quiz 1 p following 589 [PMID: 17906612 DOI: 10.1038/ncprheum0616]

37   **Sitkovsky MV**. T regulatory cells: hypoxia-adenosinergic suppression and re-direction of the immune response. *Trends Immunol* 2009; **30**: 102-108 [PMID: 19201652 DOI: 10.1016/j.it.2008.12.002]

38   **Buckley CD**, Pilling D, Lord JM, Akbar AN, Scheel-Toellner D, Salmon M. Fibroblasts regulate the switch from acute resolving to chronic persistent inflammation. *Trends Immunol* 2001; **22**: 199-204 [PMID: 11274925]

39   **Fu X**, Li H. Mesenchymal stem cells and skin wound repair and regeneration: possibilities and questions. *Cell Tissue Res* 2009; **335**: 317-321 [PMID: 19034523 DOI: 10.1007/s00441-008-0724-3]

40   **Gauglitz GG**, Jeschke MG. Combined gene and stem cell therapy for cutaneous wound healing. *Mol Pharm* 2011; **8**: 1471-1479 [PMID: 21657247 DOI: 10.1021/mp2001457]

41   **Aller MA**, Arias JI, Arias J. Pathological axes of wound repair: gastrulation revisited. *Theor Biol Med Model* 2010; **7**: 37 [PMID: 20840764 DOI: 10.1186/1742-4682-7-37]

42   **Selman M**, Pardo A, Kaminski N. Idiopathic pulmonary fibrosis: aberrant recapitulation of developmental programs? *PLoS Med* 2008; **5**: e62 [PMID: 18318599 DOI: 10.1371/journal.pmed.0050062]

43   **Adzick NS**, Longaker MT. Scarless fetal healing. Therapeutic implications. *Ann Surg* 1992; **215**: 3-7 [PMID: 1731647]

44   **Longaker MT**, Whitby DJ, Ferguson MW, Lorenz HP, Harrison MR, Adzick NS. Adult skin wounds in the fetal environment heal with scar formation. *Ann Surg* 1994; **219**: 65-72 [PMID: 8297179]

45   **Ferguson MW**, Whitby DJ, Shah M, Armstrong J, Siebert JW, Longaker MT. Scar formation: the spectral nature of fetal and adult wound repair. *Plast Reconstr Surg* 1996; **97**: 854-860 [PMID: 8628785]

46   **Redd MJ**, Cooper L, Wood W, Stramer B, Martin P. Wound healing and inflammation: embryos reveal the way to perfect repair. *Philos Trans R Soc Lond B Biol Sci* 2004; **359**: 777-784 [PMID: 15293805]

47   **Wulff BC**, Parent AE, Meleski MA, DiPietro LA, Schrementi ME, Wilgus TA. Mast cells contribute to scar formation during fetal wound healing. *J Invest Dermatol* 2012; **132**: 458-465 [PMID: 21993557 DOI: 10.1038/jid.2011.324]

48   **Arias JI**, Aller MA, Prieto I, Arias A, de Julian Z, Yang H, Arias J. The Amazing Power of Cancer Cells to Recapitulate Extraembryonic Functions: The Cuckoo's Tricks. *J Oncol* 2012; **2012**: 521284 [PMID: 21969829 DOI: 10.1155/2012/521284]

49   **De Miguel MP**, Arnalich Montiel F, Lopez Iglesias P, Blazquez Martinez A, Nistal M. Epiblast-derived stem cells in embryonic and adult tissues. *Int J Dev Biol* 2009; **53**: 1529-1540 [PMID: 19757397 DOI: 10.1387/ijdb.072413md]

50   **Romen JW**, Lütjen-Drecoll E. Funktionell Embryology. Sttutgart: Schattauer, 2006: 1-37

51   **Jauniaux E**, Gulbis B. Fluid compartments of the embryonic environment. *Hum Reprod Update* 2000; **6**: 268-278 [PMID: 10874572 DOI: 10.1093/humupd/6.3.268]

52   **Calleja-Agius J**, Jauniaux E, Muttukrishna S. Inflammatory cytokines in maternal circulation and placenta of chromosomally abnormal first trimester miscarriages. *Clin Dev Immunol* 2012; **2012**: 175041 [PMID: 21977049 DOI: 10.1155/2012/175041]

53   **Uberti MG**, Pierpont YN, Ko F, Wright TE, Smith CA, Cruse CW, Robson MC, Payne WG. Amnion-derived cellular cytokine solution (ACCS) promotes migration of keratinocytes and fibroblasts. *Ann Plast Surg* 2010; **64**: 632-635 [PMID: 20395817 DOI: 10.1097/SAP.0b013e3181c39351]

54   **Bellini C**, Boccardo F, Bonioli E, Campisi C. Lymphodynamics in the fetus and newborn. *Lymphology* 2006; **39**: 110-117 [PMID: 17036631]

55   **Shaw SW**, David AL, De Coppi P. Clinical applications of prenatal and postnatal therapy using stem cells retrieved from amniotic fluid. *Curr Opin Obstet Gynecol* 2011; **23**: 109-116 [PMID: 21386681 DOI: 10.1097/GCO.0b013e32834457b1]

56   **Fraser ST**, Baron MH. Embryonic fates for extraembryonic lineages: New perspectives. *J Cell Biochem* 2009; **107**: 586-591 [PMID: 19415688 DOI: 10.1002/jcb.22165]

57   **Gulbis B**, Jauniaux E, Cotton F, Stordeur P. Protein and enzyme patterns in the fluid cavities of the first trimester gestational sac: relevance to the absorptive role of secondary yolk sac. *Mol Hum Reprod* 1998; **4**: 857-862 [PMID: 9783845]

58   **Siegel N**, Rosner M, Hanneder M, Freilinger A, Hengstschläger M. Human amniotic fluid stem cells: a new perspective. *Amino Acids* 2008; **35**: 291-293 [PMID: 17710362 DOI: 10.1007/s00726-007-0593-1]

59   **Nakazawa F**, Alev C, Jakt LM, Sheng G. Yolk sac endoderm is the major source of serum proteins and lipids and is involved in the regulation of vascular integrity in early chick development. *Dev Dyn* 2011; **240**: 2002-2010 [PMID: 21761483 DOI: 10.1002/dvdy.22690]

60   **Bevilacqua E**, Hoshida MS, Amarante-Paffaro A, Albieri-Borges A, Zago Gomes S. Trophoblast phagocytic program: roles in different placental systems. *Int J Dev Biol* 2010; **54**: 495-505 [PMID: 19757392 DOI: 10.1387/ijdb.082761eb]

61   **Knöfler M**. Critical growth factors and signalling pathways controlling human trophoblast invasion. *Int J Dev Biol* 2010; **54**: 269-280 [PMID: 19876833 DOI: 10.1387/ijdb.082769mk]

62   **Aller MA**, Arias JI, Prieto I, Gilsanz C, Arias A, Yang H, Arias J. Surgical inflammatory stress: the embryo takes hold of the reins again. *Theor Biol Med Model* 2013; **10**: 6 [PMID: 23374964 DOI: 10.1186/1742-4682-10-6]

63   **Eisenhut M**. Changes in ion transport in inflammatory disease. *J Inflamm* (Lond) 2006; **3**: 5 [PMID: 16571116 DOI: 10.1186/1476-9255-3-5]

64   **Crivellato E**, Nico B, Ribatti D. The chromaffin vesicle: advances in understanding the composition of a versatile, multifunctional secretory organelle. *Anat Rec* (Hoboken) 2008; **291**: 1587-1602 [PMID: 19037853 DOI: 10.1002/ar.20763]

65   **Lepperdinger G**. Inflammation and mesenchymal stem cell aging. *Curr Opin Immunol* 2011; **23**: 518-524 [PMID: 21703839 DOI: 10.1016/j.coi.2011.05.007]

66   **Kunisaki Y**, Frenette PS. The secrets of the bone marrow niche: Enigmatic niche brings challenge for HSC expansion. *Nat Med* 2012; **18**: 864-865 [PMID: 22673997 DOI: 10.1038/nm.2825]

67   **Li H**, Fu X. Mechanisms of action of mesenchymal stem cells in cutaneous wound repair and regeneration. *Cell Tissue Res* 2012; **348**: 371-377 [PMID: 22447168 DOI: 10.1007/s00441-012-1393-9]

68   **Koh TJ**, DiPietro LA. Inflammation and wound healing: the role of the macrophage. *Expert Rev Mol Med* 2011; **13**: e23 [PMID: 21740602 DOI: 10.1017/S1462399411001943]

69   **Brancato SK**, Albina JE. Wound macrophages as key regulators of repair: origin, phenotype, and function. *Am J Pathol* 2011; **178**: 19-25 [PMID: 21224038 DOI: 10.1016/j.ajpath.2010.08.003]

70   **Bayless KJ**, Johnson GA. Role of the cytoskeleton in forma-

tion and maintenance of angiogenic sprouts. *J Vasc Res* 2011; **48**: 369-385 [PMID: 21464572 DOI: 10.1159/000324751]

71   **Otto WR**, Wright NA. Mesenchymal stem cells: from experiment to clinic. *Fibrogenesis Tissue Repair* 2011; **4**: 20 [PMID: 21902837 DOI: 10.1186/1755-1536-4-20]

72   **De Miguel MP**, Fuentes-Julián S, Blázquez-Martínez A, Pascual CY, Aller MA, Arias J, Arnalich-Montiel F. Immuno-suppressive properties of mesenchymal stem cells: advances and applications. *Curr Mol Med* 2012; **12**: 574-591 [PMID: 22515979]

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