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Role of Growth Factors in Inflammation and Repair

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Mononuclear cells generate a variety of hormone-like proteins termed growth factors that are instrumental in the evolution and resolution of inflammatory reactions. Many of these growth regulatory molecules have multifunctional properties. For example, the mononuclear cell-derived growth factors, platelet-derived growth factor (PDGF), and transforming growth factor beta (TGF-β), are potent leukocyte chemoattractants. In addition, TGF-β, a product of platelets, T lymphocytes, and monocytes, appears to induce the transcription of other monocyte-derived growth hormone genes. In this regard, picomolar concentrations of TGF-β stimulate peripheral blood monocytes to transcribe the genes for PDGF (c-sis), basic fibroblast growth factor (FGF), interleukin 1 (IL-1), and tumor necrosis factor (TNF). Furthermore, levels of mRNA for TGF-β, which is constitutively expressed in resting monocytes, are also increased by exogenous TGF-β. Each of these monocyte products exhibits a plethora of biological activities on other cell types. T lymphocytes, in response to antigen, contribute to this network by secreting growth factors and lymphokines that regulate monocyte growth factor production.

Key words: mononuclear cells, tissue repair, leukocyte chemoattractants

Recruitment of mononuclear cells to sites of inflammation and injury is accompanied by their activation, proliferation, and/or the release of soluble factors that orchestrate subsequent inflammatory events. Mononuclear cells and their products are central to the events of inflammation and wound healing as suggested by Leibovich and Ross in 1975 [1]. Among the soluble factors released by monocytes and lymphocytes are a series of polypeptide growth factors involved in the regulation of inflammation, tissue repair, fibrotic diseases, atherogenesis, cancer, and developmental processes.

For the most part, secretion of growth factors by inflammatory cells is dependent upon activation. Once activated by infectious agents, other antigens, or tissue injury, these cells generate numerous factors that promote local inflammation as well as the recruitment, proliferation and function of fibroblasts and endothelial cells (reviewed in [2]). Since both T lymphocytes and macrophages produce cytokines capable of regulating endothelial cell and fibroblast growth and function, these cytokines likely contribute

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TABLE I. Inflammatory Cell-Derived Peptide Growth Factors

	Lymphocytes	Monocytes
IL-1		+
PDGF		+
TGF-α		+
TGF-β	+	+
FGF(b)		+
TNF-α	+	+
TNF-β (LT)	+	
IP-10	+	
FAF	+	

to the link between inflammation and repair. Since these cytokines may be instrumental in the final resolution of an inflammatory response, they are the focus of this brief review.

Tissue repair begins as the host sequesters and/or degrades the inflammatory stimulus. Cellular elements necessary for tissue repair move into the inflammatory site and proliferate. Although mesenchymal cell accumulation becomes visibly apparent only in the later phases of the inflammatory response, the stage was being set for these events from the very beginning of the inflammatory response. Inflammatory mediators and/or growth factors released by the complement system, activated platelets, and endothelial cells contribute to mesenchymal cell recruitment and proliferation. As monocytes and lymphocytes accumulate in the lesions, they generate additional chemotactic factors that recruit fibroblasts [2]. Expansion of the fibroblast population is the result not only of recruitment of fibroblasts to the lesion, but also the consequence of proliferation owing to locally generated fibroblast growth factors.

Although proliferation is influenced by a host of agents, the most critical are the polypeptide growth factors (Table I).Of these, interleukin-1 (IL-1), originally described as an activator of lymphocyte proliferation and an endogenous pyrogen [3,4], has subsequently been shown to possess a vast array of biological activities [5]. The cDNAs for IL-1α and β encode 31,000 dalton, 269 amino acid precursor molecules that are proteolytically cleaved into the 17,000 dalton biologically active forms [6,7]. Numerous activities have been attributed to these structurally distinct, but functionally similar peptides including the regulation of certain connective tissue functions. Fibroblast proliferation [8], arachidonic acid metabolism [9], and the synthesis of collagen [10], collagenase [11], and hyaluronic acid [12] are all stimulated by IL-1. Recent evidence indicates that the production of IL-1 is not restricted to monocytes and macrophages, but that IL-1 is generated by a diverse spectrum of circulating and fixed cells, thereby suggesting its central role in coordinating inflammatory and immunologic events (reviewed in [13]).

Macrophages also secrete other peptide factors that regulate connective tissue function, including tumor necrosis factor-alpha (TNF-α) or cachectin. Although there appears to be only a 3% amino acid sequence homology between TNF-α and IL-1β, many of its biological properties overlap including those relating to the acute phase and wound healing responses. In the inflammatory and wound healing process, TNF-α, like IL-1, promotes fibroblast proliferation [14,15], collagen and collagenase biosynthesis, and PGE_2 release [16,17]. Although TNF-α is an inhibitor of vascular endothelial cell growth in vitro, it promotes angiogenesis and new blood vessel formation in vivo [18,19] contributing to the reparative phase of inflammation.

Another macrophage product that likely contributes to the reparative phase of inflammation is transforming growth factor alpha (TGF-α), which can augment mesenchymal and endothelial cell growth [20]. Recently demonstrated to be produced by activated macrophages [21], this peptide, which ranges in size from 5,000 M_r to 20,000 M_r [20], interacts with the same cellular receptor as epidermal growth factor [22]. Of significance is the identification of TGF-α mRNA by polymerase chain reaction amplification in adherent cells with macrophage-specific antigens isolated from a wound site [23] favoring a role for this peptide in the healing process.

Platelet-derived growth factor (PDGF), originally described as a product of platelets, is also synthesized and secreted by activated macrophages [24,25]. PDGF is a 32,000 dalton dimeric glycoprotein consisting of an A chain (14,000 M_r) and a B chain (17,000 M_r), which share approximately 60% sequence homology [26,27] and are linked by two disulfide bonds [28,29]. At low concentrations, PDGF displays chemotactic properties for neutrophils, macrophages, and fibroblasts [30,31]. Following recruitment, PDGF also serves as a mitogenic signal for fibroblasts [32], promotes collagen biosynthesis [33], and increases collagenase release [34]. The biological action of PDGF is initiated at the cellular level by binding to a high affinity cell-surface receptor that appears to be a tyrosine-specific protein kinase [35–37]. The fibroblast-stimulating and chemotactic activities appear to be related to separate structural sites on the PDGF peptide backbone [38]. Whereas platelets provide the initial source of PDGF at sites of tissue injury, the macrophages are likely responsible for the continued generation of this growth factor.

Similar to PDGF, fibroblast growth factor (FGF), with significant proliferative capacity for endothelial cells and fibroblasts [39], was characterized from another source (brain) long before it was recognized as a monocyte product [40]. Synthesis of basic FGF (bFGF), which shares sequence homology with IL-1 [41], is regulated at the pretranslational level in activated macrophages [42]. Hybridization of RNA derived from activated monocytes with a bFGF cDNA probe revealed increased steady state levels of FGF mRNA transcripts above those seen in unstimulated cells. Thus monocytes can be induced to express the gene for FGF and to synthesize this potent mitogenic factor. In addition to proliferation, bFGF can regulate the synthesis and deposition of extracellular matrix components including collagen, fibronectin, and proteoglycans. Since bFGF can also induce endothelial cells to migrate and organize into tubules, the precursors of new blood vessels [43], FGF may be an important macrophage product for the angiogenic and fibrogenic response associated with wound healing.

One of the most effective inducers of IL-1, TNF, PDGF, and FGF gene expression in monocytes is transforming growth factor beta (TGF-β), a 25,000 M_r peptide released by platelets [44], lymphocytes [45] and also secreted by macrophages upon activation [46]. Structurally, TGF-β is a homodimer composed of two disulfide-linked 112 amino acid chains [47]. The gene for TGF-β is transcribed into a 2.5 kb mRNA which is constitutively present in monocytes [46] and must be induced in lymphocytes [45]. Although mRNA is constitutively expressed by monocyte-macrophages, the cells require activation to synthesize and secrete the TGF-β polypeptide. Since the levels of mRNA for TGF-β are not increased in activated monocytes, it is likely that different intracellular mechanisms regulate gene expression and secretion of TGF-β in this cell population. Significantly, the secretion of TGF-β by activated macrophages, and the ability of TGF-β itself to activate macrophages [42] suggest an important autocrine

and/or paracrine loop for regulation of monocyte-derived growth factors essential to fibroblast proliferation and repair.

Essentially all cell types have high affinity receptors for TGF-β [48], indicating the potential widespread influence of this molecule. TGF-β appears to have a particularly important role in the process of inflammation and tissue repair. In this regard, injection of TGF-β subcutaneously into newborn mice induces rapid fibrosis and angiogenesis in the form of granulation tissue [49]. This is likely due to the ability of TGF-β to stimulate monocyte-macrophage chemotaxis, which may be a determining factor for the precise migratory progression of inflammatory cells into the tissue. Within the inflammatory lesion, monocytes recruited by TGF-β are further stimulated by locally higher concentrations of TGF-β to synthesize and secrete other growth factors such as FGF, PDGF, TNF, and IL-1 [42,50]. The inflammatory response is thereby augmented and the stage for fibroblast and endothelial cell recruitment, proliferation, and matrix synthesis is set. Thus, TGF-β may be pivotal in inflammation and tissue repair. TGF-β can also stimulate chemotaxis [51] and proliferation [52] of fibroblasts. Moreover, collagen [49], fibronectin [53], and proteoglycan [54] synthesis are stimulated at the level of mRNA transcription [55] resulting in increased matrix deposition.

TGF-β, while promoting tissue repair, is a potent inhibitor of T cell proliferation [45,56]. The exact mechanism by which this inhibition occurs is not clear since production of the lymphocyte growth factor, interleukin-2, or its receptor is not affected in the T cells [56]. Since TGF-β stimulates macrophages to synthesize IL-1, TGF-β may serve as a negative feedback mechanism in order to inhibit the inflammatory response while continuing to modulate tissue repair.

Although it inhibits T cell growth, TGF-β does not appear to prevent cytokine synthesis and indeed, T cells secrete TGF-β in response to antigen during an inflammatory response. TGF-β production by lymphocytes, unlike monocytes, is dependent upon activation for gene expression, synthesis, and secretion [45]. The production of this multipotential mediator by platelets, monocytes, and lymphocytes clearly indicates its central role in immunological events. T lymphocytes synthesize and secrete other cytokines that regulate fibroblast growth. Among these cytokines are TNF-α and lymphotoxin (TNF-β), which appear to be indistinguishable in their growth regulatory properties for mesenchymal cells and in their ability to regulate matrix generation [57]. The generation of gamma interferon (γIFN) by activated T cells may influence tissue repair both directly and indirectly. Direct stimulation of fibroblast growth has been reported [58], but γIFN is also a potent regulator of monocyte-macrophage growth factor production [59]. IFN enhances transcription of TNF and IL-1, as well as IP-10, a 10,000 M_r protein with significant homology to a family of chemotactic and mitogenic proteins [60]. Another T cell product, fibroblast activating factor (FAF) is produced by T lymphocytes following stimulation with specific antigens or T cell mitogens in vitro [61]. This mediator, which is distinct from IL-2, IL-1, TNF-β, and γIFN, has a molecular weight of 35–40,000 daltons and induces proliferation of a quiescent population of nonconfluent fibroblasts under serum-free conditions [62]. Furthermore, FAF has been identified as one of the products spontaneously secreted by mononuclear cells in chronic inflammatory lesions in which fibroblast proliferation is a hallmark of the pathologic process [63,64].

Associated with the accumulating population of fibroblasts is the observed deposition of connective tissue matrix. Recruited fibroblasts are stimulated by inflammatory

TABLE II. Fibrosis Associated With Immune Cells

Tuberculosis
Schistosomiasis
Pulmonary fibrosis
Scleroderma
Sarcoidosis
Chronic hepatitis
Rheumatoid arthritis

cell-derived molecular signals to increase their synthetic activities with the generation of extracellular connective tissue matrix proteins. As indicated, many of the polypeptide factors that regulate cell division also influence protein synthesis. TNF, IL-1, and TGF-β upregulate the synthesis of fibrillar proteins (collagen) and of proteoglycans and glycoproteins (fibronectin, laminin, and chondronectin), which constitute the ground substance of the extracellular matrix [12].

Whereas manifestations of normal tissue repair are represented by simple scar formation, the prolonged release of growth-promoting and matrix-inducing factors in certain inflammatory responses may result in excessive accumulation of fibroblasts and extensive collagen deposition with potentially pathological consequences (Table II) [2]. Mechanisms whereby mononuclear cells suppress matrix synthesis have also been identified [65,66], although it is not entirely clear what determines continuation versus termination of the synthesis of collagen and other matrix proteins. One regulatory element is likely provided by the production of IFN, which inhibits collagen synthesis at the transcriptional level [67].

Understanding the events associated with physiologic wound healing and scar formation and how they are regulated may enable us to define the pathology of disease states associated with unresolved inflammation and fibrosis. Furthermore, these investigations may also reveal approaches that can be used to modify or control the repair process. Since cell proliferation is central to inflammation and repair, the immune cell-derived growth factors may be important targets for regulating and controlling these processes.

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