Stromal cells as new therapeutic targets in rheumatoid arthritis

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Rheumatoid arthritis is a painful, debilitating disease in which inflammation is localized mainly to synovial joints. Despite a plethora of therapies targeted at inflammatory cells such as lymphocytes, there has been little impact made on affecting a cure. Even with the most effective current treatments (antitumor necrosis factor-α agents), only about 50% of patients gain a 70% response as measured by conventional disease activity criteria (ARC 70). In recent years, stromal cells that define the microenvironment in which inflammation occurs have been shown to play an important role in the pathogenesis of rheumatoid arthritis, especially during the switch from acute to chronic persistent disease. In this review, the role that stromal cells, such as endothelial cells, fibroblasts and macrophages play in the pathogenesis of rheumatoid arthritis are examined, and it is suggested that these cells in addition to inflammatory immune cells provide an important and underappreciated therapeutic target.

The architecture of organs and tissues are closely adapted to their function such that they provide specialized microenvironments in which to carry out their functions efficiently. The nature and character of such microenvironments are primarily defined by the stromal cells that reside within the tissues. A stromal cell can be considered as a cell that aids in defining the very nature of the tissue microenvironment by the production of an extracellular matrix (ECM) and cytokine milieu that primarily provide a landscaping supporting tissue structure and integrity [1]. They are nonhemopoietic and resistant to radiation such as epithelial cells, fibroblasts and endothelium, but can also include tissue-specific macrophages that originate in the bone marrow. For example, tissue macrophages in the liver (Kupffer cells) and lung (alveolar macrophages) perform very different functions compared with macrophages in the brain (glial cells) or skin (Langerhans cells), yet are all members of the monocyte/macrophage family.

Stromal cells are responsible for helping to organize tissues, and in specialized niches such as the bone marrow, enable hemopoietic cells to proliferate and differentiate appropriately. Defects in stromal cell function can lead to the impairment of organ function and have been strongly associated with tumorigenesis (for two excellent reviews see [2,3]). However the contribution of stromal cells to inflammation has only recently become recognized. For example, fibroblasts are important contributors to the inflammatory response, helping to define the type and duration of response [1]. In a normal inflammatory response, once the infiltrating leukocytes are no longer required, loss of survival signals and the normalization of chemokine gradients that attract cells into the site of inflammation results in the death and emigration of inflammatory cells out of the tissue. This switch to resolution is an important signal that allows tissue repair to take place and enables immune cells to return to draining lymphoid tissues (lymph nodes) in order for immunologic memory to become established [4]. However, in immune-mediated inflammatory diseases such as rheumatoid arthritis (RA), stromal cells contribute to the inappropriate recruitment and retention of leukocytes, leading to chronic, persistent inflammation that ultimately results in destruction of the joint [5]. In this review we examine how the aberrant temporal and spatial expression of cytokines and chemokines by stromal cells within the synovium contribute to pathology and suggest that these processes present attractive targets for therapeutic intervention.

Rheumatoid arthritis

RA is a chronic, persistent, immune-mediated inflammatory disease that manifests clinically as synovitis and tissue hyperplasia of diarthroidal joints. It involves classically the small joints of the hands and feet in a symmetrical pattern [6]. Annually, RA affects 10–20/100,000 males and 20–40/100,000 females. Despite the use of effective anti-inflammatory agents and disease-modifying drugs, a significant proportion of

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patients with RA continue to possess drug-resistant disease. Complete clinical remission is unusual for more than 6 months and a formal cure of the disease remains elusive [7].

The etiology of RA remains an enigma. There is a modest genetic association with different populations around the world having prevalence rates of between 0.5 and 1% which has led to suggestions that RA is caused by an infective agent [8,9]. Some support for this concept has arisen from studies demonstrating that alleles of the major histocompatibility complex (MHC) II gene also have a considerable genetic influence over the severity of disease, with people possessing human leukocyte antigen (HLA) DR4 being most susceptible to destructive forms of RA [10,11]. The fact that these HLA specificities are associated with RA does not necessarily imply that infections are a cause of RA or that self-reactive immune cells elicit or even perpetuate the disease. In fact, recent studies have provided alternative and potentially more exciting explanations for the HLA link with autoimmune diseases such as RA [12]. In this model, the HLA association does not predispose to disease, but rather is associated with a failure to protect from an over-reactive immune response and with a prematurely aging immune system [13,14].

These alternative explanations provide elegant explanations for the puzzling lack of antigen-specific T-cell responses in RA. Moreover, they have caused researchers to refocus their efforts more on the reasons why synovial inflammation persists in RA rather than why it occurs in the first place.

Cellular organization of the inflamed synovium in RA

The synovium is a soft tissue which in healthy people lines the noncartilaginous surfaces of diarthroidal joints and tendon sheaths [15,16]. It is composed of surface layers and a specialized matrix known as the intimal and the subintima, respectively. The cells of the intimal lining layer are composed of two types; macrophage-like cells (type A synoviocytes) and fibroblast-like cells (type B synoviocytes). Normally, the intimal layer is only 1-3 cells thick, but in patients suffering from RA, it becomes hypertrophied and edematous with synovial tissue invading the underlying cartilage and bone (**Figure 1**) [16,17].

Accompanying the hypertrophy of the synovial lining cells is a mixed leukocyte infiltration composed of T-cells, B cells, macrophages, neutrophils and dendritic cells (DCs). These infiltrating cells are often organized into three main patterns:

- A diffuse distribution throughout the synovium
- Perivascular cuffs of leucocytes
- Organized lymphoid structures that in some cases resemble lymphoid follicles typically seen within lymphoid tissue [18]

It remains unclear whether these patterns predict outcome or response to particular therapies, but it has been suggested that the presence of organized lymphoid follicles predicts more aggressive, persistent disease which may respond better to anti-tumor necrosis factor (TNF) therapies compared with patterns with a diffuse inflammatory infiltrate [19].

Contribution of fibroblasts to inflammation in RA

Stromal cells (endothelial cells, fibroblasts and macrophages) play an essential role as sentinel cells within tissues and are the first cells that respond to danger/damage signals [20]. Fibroblasts are a ubiquitous cell population found in every tissue and organ throughout the body. For many years their function was thought to be simply to produce the ECM and provide structural support for tissues [21]. It has only recently been appreciated that fibroblasts play an active role in regulating the immune response by providing the 3D context in which the inflammatory response occurs [19,22]. In RA, as in a range of other immune-mediated inflammatory diseases, fibroblasts contribute to an environment which results in the aberrant accumulation of cells within the joint [5]. Arguably, the contribution of synovial fibroblasts to the pathogenesis of RA can be demonstrated by the fact that synovectomy of the inflamed synovia does halt progression of the disease. However, by the time a synovectomy is performed, much of the destruction of the joint has already occurred and it is not an ideal treatment as therapeutic intervention should aim to prevent the onset of the disease before it reaches this stage.

Fibroblasts have traditionally been described as being derived from cells of the mesenchymal lineage [23]. However, the developmental origin of fibroblasts has been challenged by recent findings suggesting that in some tissues they appear to develop from epithelial precursors as a result of epithelial to mesenchymal transition (EMT). EMT occurs in tumor cells undergoing metastasis and during development [24]. For example, fibroblasts can emerge from epithelial cells in experimental models of kidney disease and lead to fibrosis [24,25]. This process of

Highlights

- Despite spectacular advances in the development of current therapies only about 50% of patients gain remission as measure by conventional disease activity scores.
- Aberrant stromal cell function remains relatively resistant to manipulation by current therapies.
- The etiology of RA remains enigmatic, but fibroblasts appear to play an important role in the persistence of the disease.
- The pattern of leucocyte accumulation within the rheumatoid synovium may predict response to therapy.
- Fibroblasts play a key role in providing the 3D context in which the inflammatory response occurs.
- Fibroblasts display an inappropriately activate phenotype in rheumatoid arthritis.
- Antagonism of the stromal derived chemokine SDF-1 (CXCL12) has been shown to have beneficial effects in mouse models of RA.
- Naturally occurring, stromally derived anti-inflammatory lipid mediators (lipoxins/resolvins) are exciting new anti-inflammatory targets.

molecules – suitably termed resolvins – are derived from omega-3 fatty acids and are potent inhibitors of neutrophil migration and the release of cytokines [65,66]. It therefore seems likely that the therapeutic manipulation of members of the resolvin and liopxin families will provide novel and mechanistically distinct anti-inflammatory pathways for targeting. Exciting new data has shown that the administration of anti-inflammatory lipid mediators such as lipoxins have potent anti-inflammatory properties in asthma [67].

Expert opinion

In this review we have demonstrated that stromal cells within tissues play a pivotal role in the switch to persistence in chronic synovial inflammation that lies at the heart of RA. Stromal cell play a vital role in choreographing cellular infiltrates in tissue. This is needed for the organization of healthy tissues, but in diseases such as RA, the aberrant behavior of stromal cells has deleterious consequences; producing an environment that causes the sustained recruitment and inappropriate retention of leucocytes leading to the destruction of bone. What causes a stromal cell to change phenotype, from one that helps the resolution of inflammation to one in which drives the persistence of inflammation is not known at present and the search to the answer to this question will provide the impetus for future research into rheumatoid arthritis.

Outlook

Stromal cells such as endothelium, fibroblasts and macrophages make an attractive therapeutic target as they regulate leucocyte entry into and within tissues and are key orchestrators of the inflammatory cell infiltrate. The resolution of inflammation is an often ignored phase of the inflammatory response. Most current therapies target attempt to inhibit the production and function of pro-inflammatory mediators involved in the initiation and development of inflammation. An alternative target for therapeutic intervention is the active induction of mediators involved in the resolution of inflammation. As many of these naturally occurring anti-inflammatory agents are made by stromal cells during an acute inflammatory response, it is likely that these cells will become increasingly important therapeutic targets in the future.

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