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Review

Bone marrow contributions to fibrosis☆

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ABSTRACT

Bone marrow transplant experiments in mice using labelled donor bone marrow have indicated that following injury bone marrow derived cells can circulate and home to the injured organs. In particular fibrocytes and myofibroblasts are capable of contributing to the wound healing response, including collagen deposition. In chronic injury this can lead to a pathological degree of fibrosis. Experiments have shown that this can be a relatively insignificant contribution to the scar forming population in certain organs and that the majority of the scar forming cells are intrinsic to the organ. Conversely, in certain circumstances, the circulating cells become major players in the organs fibrotic response. Whilst cell tracking experiments are relatively simple to perform, to actually determine a functional contribution to a fibrotic response more sophisticated approaches are required. This can include the use of bone marrow transplantation from recipients with collagen reporter systems which gives a read out of bone marrow derived cells that are transcriptional active for collagen production in a damaged organ. Another technique is to use bone marrow transplants from donors that have a mutation in the collagen to demonstrate a functional difference in fibrosis when bone marrow transplants performed. Recent reports have identified factors mediating recruitment of circulating fibrocytes to injured organs, such as CXCL12 and CXCL16 and shown that blocking these factors reduced fibrocyte recruitment and subsequent fibrosis. The identification of such factors may enable the development of novel therapies to block further fibrocyte engraftment and fibrosis in situations of pathological scarring. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

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1. General considerations—what techniques are used to assess the evidence for the bone marrow (BM) contributing to organ fibrosis?

In this section we will discuss the evidence for BM derived cells contributing to organ fibrosis. To understand the techniques that have been used to assess contribution of BM derived cells to fibrogenesis in injured organs it is worth briefly reviewing the stem cell composition of the BM.

2. The composition of the BM

2.1. The haematopoietic stem cells

The haematopoietic stem cells (HSCs) residing within the BM are multipotent and are the source of the myeloid and lymphoid populations of the blood. Haematopoietic stem cells are radiation sensitive and therefore can be studied accurately using a protocol in mice of lethal irradiation which ablates the endogenous haematopoietic stem cells, followed by injection of haematopoietic cells that are labelled or traceable in some manner. This can be through the use of genetically marked BM such as green fluorescent protein (GFP) labelled BM, sex-chromosome markers (where the recipient mice are female, XX and the donors male, XY) or other technologies. The donor haematopoietic stem cells can be purified and sorted with specific markers, following peripheral vein injection are able to engraft the irradiated recipients BM and then differentiate into the progeny of haematopoietic stem cells providing long term repopulation of all the blood lineages. The application of known doses of irradiation can produce recipient BM where practically all of the haematopoietic system is of donor origin and this can be easily checked using FACS (e.g. for GFP). Analysis of the engraftment and functional effects of the progeny of haematopoietic stem cells in injured organs is therefore relatively straightforward.

Abbreviations: BM, bone marrow; CP, chronic pancreatitis; (EOG-EPC)s, early outgrowth endothelial progenitor cells; GFP, green fluorescent protein; hSAP, human serum amyloid protein; (LOG-EPC)s, late outgrowth endothelial progenitor cells; MSCs, mesenchymal stem cells; HSCs, haematopoietic stem cells; EPCs, endothelial progenitor cells; ARDS, acute respiratory distress syndrome; NASH, non-alcoholic steatohepatitis; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; AMD, age related macular degeneration; FSGS, focal segmental glomerulosclerosis

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2.2. Fibrocytes

Fibrocytes are inactive precursors of the collagen secreting fibroblasts. Circulating fibrocytes have been identified in the blood that are CD34+, CD45+, collagen-1+. These fibrocytes are thought to be able to circulate in the blood, differentiate into fibroblasts and contribute to collagen accumulation in injured organs [1]. Fibrocytes have been implicated in fibrogenesis in the skin, lung, liver and kidney and are characterised as expressing haematopoietic markers (CD11b, GR1, CD45) as well as markers of cell adhesion (CD54) and co-stimulatory molecules CD80 and CD86 and secrete pro-fibrotic cytokines and growth factors (TGF-b and MCP-1). Fibrocytes are recruited to injured organs via a variety of cytokines and chemokines and recruitment can be inhibited in mice deficient in chemokine receptors particularly CCR2, CXCR4 and CCR5 in the lung [2,3] and CCR2, CCR7 and CXCR4 in the kidney [4]. Human serum amyloid protein (hSAP) is a natural inhibitor of fibrocyte differentiation and maturation [5]. Mice treated with hSAP develop less fibrosis in response to injury in several organs and have been successfully tested in limited clinical trials in patients with skin, kidney and lung fibrosis [6–10], suggesting an important role for these cells in pan-organ fibrosis.

2.3. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are capable of tri-lineage differentiation into osteoblasts, chondrocytes, and adipocytes [11]. MSCs are classified by the expression of mesenchymal markers CD105, CD90 and CD73, and lack of expression of haematopoietic markers CD45, CD34, CD14 and CD11b and are thus distinct from fibrocytes which express CD45 and CD11b. As well as their regeneration effects, MSCs are also thought to modulate disease progression via their anti-inflammatory and immune-modulatory properties and secrete a variety of mediators such as TGF-β, IL-10, prostaglandins and indolamine 2, 3-dioxegenase and support the development of regulatory T cells [11–15]. In addition the effects and functional properties of MSCs may be influenced by the inflammatory milieu and can adopt a pro-inflammatory MSC1 and anti-inflammatory MSC2 phenotype, similar to that adopted by macrophages [16]. Several studies have reported that MSCs from patients exhibit a completely recipient profile after total body irradiation and BM transplantation, whereas HSCs are of donor origin [17,18] suggesting that MSCs in their niches are likely to be radio-resistant. Furthermore in the experimental setting, when using standard irradiation and BM transplant procedures in mice and rats, the resident promising population is unaffected by irradiation, unlike the HSC population which becomes of donor origin. Therefore it is not straightforward to determine whether MSCs contribute to organ fibrosis in disease states. It is worth considering their fibrogenic potential either in disease, or perhaps of more relevance, following the injection of exogenous MSCs as these cells are being considered for use in cell therapies in a number of diseases. The ability to isolate and expand human MSCs in culture has stimulated research into their therapeutic potential where MSCs have been expanded in culture and injected during injury models. For example MSCs have been shown to reduce fibrosis and tubular atrophy in a rat kidney allograft model [19] and have beneficial effect in myocardial infarction, lung fibrosis and acute liver injury [20–22]. Thus MSCs may have potential clinical use in certain disease scenarios. The factors regulating the mobilisation of MSCs from the BM are less well understood than those factors governing HSC mobilisation. While GCSF stimulates MSC proliferation in the BM it does not stimulate mobilisation and a combination of the CXCR4 antagonist AMD3100 (which effectively mobilises HSCs) with GCSF did not mobilise MSCs [23] However, stromal progenitor cells have been mobilised from the BM in mice using a combination of CXCR4 and VEGF [23]. MSCs are currently being evaluated in several clinical trials for a variety of diseases, including Crohn's disease, multiple sclerosis, diabetes mellitus, and acute graft-vs-host disease, with some efficacy [11,24–26] but their use in fibrotic disease remains to be established.

3. Endothelial progenitor cells (EPCs)

EPCs are a population of mononuclear cells in the blood thought to be capable of differentiating into endothelial cells in vitro. These cells are suggested to contribute to angiogenesis either by directly differentiating into endothelial cells or by secreting proangiogenic factors and chemokines such as VEGF, CXCL12 and IGF-1 [27]. EPCs are cultured from blood mononuclear cells and form colonies in the presence of endothelial growth factors. Early outgrowth EPCs (EOG-EPC)s have characteristics of both endothelial and monocytic cells and express CD45, CD11c, and CD14, and the endothelial markers CD31 and VEGFreceptor-2. Late outgrowth EPCs (LOG-EPC)s express the endothelial markers and CD34 but do not express monocytic markers. The potential for EPC transplantation and therapy has been most widely studied in cardiovascular disease where transplantation of EPCs has been shown to reduce fibrosis in several models e.g. myocardial infarction [28]. However EPCs have also been shown to reverse liver fibrosis [29] and reduce portal hypertension associated with CCl_4-induced liver cirrhosis [30] and reduce obstructive renal fibrosis [31].

3.1. Tracking BM cells in human tissue

In humans, to determine the presence of BM derived cells in injured organs it has been necessary to analyse tissue from patients that have received BM transplants. Typically this has been female (XX chromosomes) patients that have received male (XY chromosomes) BM transplants where the Y chromosome denotes a human cell that can be tracked in a damaged organ using in situ hybridisation for the Y chromosome. This can be combined with immunohistochemistry for a cell type marker (e.g. such as αSMA to mark a myofibroblast) to confirm cell phenotype [32]. However, the combination of standard in situ hybridisation with immunohistochemistry analysis may not be sufficient to localise the nuclear Y chromosome in the nucleus with αSMA expression in the cytoplasm in individual cells [33]. Other approaches have involved analysing female organs that have been transplanted into male recipients for evidence of male (recipient) myofibroblasts in the organ, although this does not directly prove BM origin. These histological studies have been useful for suggesting a potential role of the BM in organ fibrosis but are of course descriptive and not functional. Furthermore, techniques such as in situ hybridization can be difficult to optimise and also need rigorous analysis with appropriate controls to prevent inappropriate conclusions being reached.

3.2. Evidence that the BM cells are synthesising and secreting collagen

The evidence that BM cells are synthesising collagen can be obtained using transgenic mice that are transcriptional reactive for collagen or express a fluorescent gene under the control of a specific promoter such as a collagen or αSMA gene [34,35]. However it is worth noting on a technical level that if one uses collagen reporter mice, this will show transcriptional activity at the time of assay (typically when tissue is harvested unless whole body live imaging is used). This may miss an earlier burst of transcriptional activity, furthermore collagen gene transcription is only part of the process required to actually deposit collagen in tissue. Another way of determining transcriptional activity for collagen is to look for RNA using collagen ribo-probes in cells that can be detected in tissue sections [36]. Using these approaches it has been shown that a small proportion of BM derived myofibroblasts in the liver are transcriptionally active for collagen. Another approach has used *in vivo* imaging to track collagen expressing fibrocytes to the liver using BM from chimeric mice expressing luciferase under control of the α1(I) collagen promoter [37]. Another study used BM transplantation from donor mice with a genetic mutation of the collagen gene.

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