26

The Fibrotic Response to Implanted Biomaterials: Implications for Tissue Engineering

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1. Introduction

The foreign body response describes the non-specific immune response to implanted foreign materials (Coleman et al., 1974; Anderson, 2001; Luttikhuizen et al., 2006). It is characterised by the infiltration of inflammatory cells to the area to destroy or remove this material, followed by the repair or regeneration of the injured tissue. However, if the foreign material cannot be phagocytosed and removed, the inflammatory response persists until the material becomes encapsulated in a dense layer of fibrotic connective tissue (Anderson, 2001) which shields it from the immune system and isolates it from the surrounding tissues.

The foreign body response has developed as a protective mechanism to limit exposure to toxic or allergenic materials, but also presents a problem for modern medicine. Biomedical devices now serve in a vast number of medical applications, including orthopedic, dental and breast implants, pacemakers, sutures, vascular grafts, heart valves, intraocular and contact lenses, controlled drug delivery devices and biosensors. This response is common to all medical devices or prostheses implanted into living tissue, and ultimately results in fibrosis or fibrous encapsulation which compromises the efficiency of the device and frequently leads to device failure (reviewed in Anderson et al., 2008). For example, the contraction of the myofibroblast-rich capsules around breast implants leads to 'implant shrinkage' (Abbondanzo et al., 1999) while encapsulating tissue prevents the diffusion of molecules to biosensors or from implanted drug delivery pumps (Anderson et al., 2008).

The response to implanted materials varies depending on their physicochemical properties (eg shape, size, surface chemistry, morphology and porosity; see Morais et al (2010) for review). Jones et al (2007; 2008) have shown that macrophage adhesion and fusion is higher on hydrophobic surfaces than hydrophilic/neutral surfaces while McBane and co-workers (McBane et al., 2011) found that compared with 2-dimensional films, 3-dimensional porous polyurethane scaffolds induced a low inflammatory, wound healing phenotype and may

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reduce the negative effects of the foreign body reaction. However despite attempts to identify non-immunogenic implant materials, or to mask surface properties of the implant material with biocompatible coatings (Quinn et al., 1995; Shive & Anderson, 1997; Draye et al., 1998; Paradossi et al., 2003), the inflammatory response cannot be completely avoided (Cao et al., 2008). This is thought to be due to the adsorption of proteins such as fibrinogen, complement and antibodies to the material immediately after implantation (Kao et al., 1999; Hu et al., 2001; Gretzer et al., 2006). Thus as outlined by Wisniewski et al (2001), the key to long-term functionality of implanted devices such as glucose sensors is modulation of the tissue response. In order to do this, it is important to first understand the mechanisms underlying the foreign body response to implanted biomaterials, the cells involved and their molecular mediators.

2. Application of the foreign body response to tissue engineering

While the foreign body response is an unwanted consequence of implantation of biomedical devices, the fibrotic response to implanted scaffold material has been investigated as a strategy for tissue engineering purposes. Sparks (1969, 1973) used the host inflammatory response to a foreign material to create living autologous tissue suitable for arterial bypass grafting. In this procedure a mandrel, composed of a smooth silicone rubber rod of desired diameter and length, covered with a large-mesh knitted dacron tube, was implanted subcutaneously near the location of the artery to be grafted. However despite intensive testing, the lack of compliance/strength of the resulting tissue, as well as the absence of an endothelial lining, resulted in unacceptably high rates of thrombosis, dilatation and aneurysm (Conte, 1998). More recently, our laboratory and others have used the peritoneal cavity as a 'bioreactor' to produce autologous tissue for replacement/repair of arteries (Campbell et al., 1999, 2000, 2008; Chue et al., 2004) and other hollow smooth muscle organs, specifically bladder, uterus, vas deferens (Campbell et al., 2008) and urethra (Gu et al., 2009). De Visscher and co-workers used a similar technique to pre-seed acellular matrix scaffolds from bovine pericardium for use as tissue engineered heart valves (De Visscher et al., 2007, 2008; Vranken et al., 2008) while Hayashida et al (2007) reported satisfactory function and mechanical properties for 'biovalves' prepared by embedding synthetic scaffolds subcutaneously for 4 weeks. This tissue has also been used as a source of growth factors to stimulate bone formation to repair a femoral bone defect in a sheep model (Lutton et al., 2009).

In the procedure described by our laboratory, sterile foreign objects of the appropriate shape are implanted into the peritoneal cavities of animals for 2-3 weeks, then the encapsulating tissue removed for grafting into the same animal. Our original studies showed that in the first 3 days after implantation of a foreign object, undifferentiated cells of bone marrow origin, either resident within the peritoneal fluid or recruited to it, encapsulated the object (Campbell et al., 2000). Most of these cells expressed the common leukocyte antigen (CD45) and had the morphological appearance of monocyte/macrophages (Campbell et al., 2000). By day 7 a distinct capsule of round cells and extracellular matrix (ECM) had formed, and by day 14 cells had elongated and organised into multilayered strata within a fibrillar matrix. Ultrastructurally, these elongated cells had the characteristics of myofibroblasts and contained large amounts of rough endoplasmic reticulum and bundles of peripherally distributed myofilaments (Campbell & Ryan, 1983; Campbell et al., 1999). A layer of

mesothelial cells was also observed to cover the developing capsule. The tissue encapsulating free-floating foreign objects in the peritoneal cavity is avascular, in contrast to tissue surrounding foreign material at other anatomical sites which is highly vascularised (Campbell & Ryan, 1983).

The capacity of cells within this myofibroblast-rich tissue capsule to differentiate further, if subject to the appropriate environmental cues, has also been demonstrated. For example, when grafted into an autologous artery to replace excised segments, they gradually (over 1-2 months) developed the characteristics of mature vascular smooth muscle cells (SMC) and expressed the smooth muscle differentiation markers smoothelin and smooth muscle myosin heavy chain isoform SM-2 (Efendy et al., 2000; Chue et al., 2004). Tissue remodelling occurred such that the grafted tissue developed morphological characteristics of the native artery, with the luminal surface of the smooth muscle tube becoming lined by endothelial-like cells, an outer 'adventitial' layer comprising fibroblasts, collagen matrix and vasa vasora also developed. SMC differentiation could be similarly induced by subjecting graft tissue to active intermittent stretch in vitro (Efendy et al., 2000). Similarly, when myofibroblast-rich capsules were grafted into bladder, vasa deferens or uterine horn, the graft tissue gradually remodelled to resemble the host organ, both structurally and functionally (Campbell et al., 2008).

3. What are myofibroblasts?

Myofibroblasts are heterogeneous cells of diverse origin with a morphology intermediate between fibroblasts and smooth muscle (Gabbiani et al., 1971; Powell et al., 1999; Hinz et al., 2007; Hinz, 2010). They are characterised by expression of the smooth muscle actin isoform (α-SM actin), the fibronectin splice variant ectodomain (ED-A FN) and synthesis of ECM proteins such as collagen I (Serini et al., 1998). During normal wound repair, myofibroblasts are transiently present at the wound site where they play essential roles in wound contraction and restoration of tissue integrity. Once the wound has regained normal structure and function, myofibroblasts disappear as a result of apoptosis (Gabbiani, 1996). However the prolonged presence of these cells leads to excessive collagen production and tissue contraction, and ultimately reduced tissue function and fibrosis (Mutsaers et al., 1997). Thus the timely appearance, differentiation and removal of myofibroblasts are critical for appropriate wound healing. However, despite the important roles played by myofibroblasts, further research is required to clarify the regulatory mechanisms controlling their proliferation, differentiation and apoptosis, and the factors that turn a normal repair process into pathology.

4. What is the origin of foreign body-induced myofibroblasts?`

Myofibroblasts were originally believed to be derived from tissue fibroblasts (Serini and Gabbiani, 1999), but there is now mounting evidence for alternative origins, depending on the tissue location and surrounding microenvironment. These include epithelial cells (via epithelial-mesenchymal transition; EMT; Iwano et al., 2002; Zeisberg et al., 2007; Kim et al., 2009), smooth muscle cells (Humphreys et al., 2010) and fibrocytes (Bucala et al., 1994; Abe et al., 2001; Quan et al., 2006). As major cellular constituents of the healthy peritoneal membrane, mesothelial cells are also thought to be a source of myofibroblasts within the

peritoneal cavity, via EMT (Pollock, 2005). Indeed intermediate cell types (co-expressing mesothelial and myofibroblast markers) have been reported in dialysis effluent and parietal peritoneum of peritoneal dialysis patients (Yanez-Mo et al., 2003; Jimenez-Heffernan et al., 2004). There is also evidence that myofibroblasts can derive from a bone marrow progenitor. Our early investigations used a chimaeric mouse model to demonstrate that cells of haematopoietic origin form the myofibroblast capsule in the peritoneal cavity (Campbell et al., 2000). These findings have been corroborated by numerous studies showing bone marrow-derived myofibroblasts in many organs including lung (Hashimoto et al., 2004; Brocker et al., 2006), stomach, oesophagus, skin and kidney (Direkze et al., 2003).

Given the prevalence of macrophage-like cells in the early tissue capsule, and the fact that myofibroblasts within this tissue can be derived from haemopoietic origin, we proposed that macrophages are a likely source of myofibroblasts in the peritoneal foreign body response. The capacity for peritoneal macrophages to transdifferentiate was first proposed by Kouri and Ancheta (1972) who demonstrated the presence of cells with intermediate morphologies between macrophages and fibroblasts within tissue capsules that formed around Epon lamina implants. Our laboratory also identified similar cells in the tissue capsule around foreign material (boiled blood clots) implanted in the peritoneal cavity (Campbell & Ryan, 1983; Mosse et al., 1985).

To further investigate this hypothesis, we used transgenic 'MacGreen' mice (in which the enhanced green fluorescent protein (EGFP) transgene is driven by the colony stimulating factor-1 receptor (*csf1r*) proximal promotor to direct myeloid-restricted expression; Sasmono et al., 2003, 2007) to show that the majority of cells recruited to encapsulate the foreign body were of myeloid (monocyte/macrophage) origin (Mooney et al., 2010). Although a small subset of $EGFP^-$ cells, comprising mainly lymphocytes and mast cells was also observed, these cells are unlikely to contribute directly to fibrotic tissue formation. Indeed Rodriguez et al (2009) showed that the foreign body response is similar in T-cell deficient mice, indicating that T lymphocytes do not play a significant role in this process.

Characterisation of the myeloid cell response by FACS analysis showed that in the early phase (day 2) there was a rapid recruitment of $EGFP^+$ $Gr1^+$ ($Ly6C^+$) subsets to the peritoneal cavity to encapsulate the foreign object; these cells are granulocytes and monocytes, similar to those described by Geissmann et al. (2003) and Sunderkotter et al. (2004) As the inflammatory response progressed, expression of Gr1 (Ly6C) was down-regulated, with concomitant up-regulation of F4/80 (indicative of mature macrophages) and the *csf1r*-EGFP transgene. Macrophages persisted throughout the period of study, such that by day 28, mature 'resident-like' macrophages ($Gr1^-$ $EGFP^{hi}$ $F4/80^{hi}$) were the predominant cell type within the tissue capsule. The $EGFP^+$ cells within the day 28 tissue capsule included many cells with spindle-shaped myofibroblastic morphology, although macrophages, multinucleated giant cells and a small number of neutrophils were also present. Foreign body giant cells are formed by fusion of macrophages (Anderson, 2000) and are considered a hallmark of the foreign body response (Jay et al., 2010). The presence of macrophages up to 28 days after foreign body implantation is in accord with a previous report by Gretzer et al. (2006) who showed increasing proportions of $ED2^+$ mature macrophages over time in exudates surrounding subcutaneous implants in rats. However in our experience, the peritoneal foreign body response is more rapid in rats than mice. In contrast to the mouse

where only a small proportion of cells express α-SM actin at day 14 (Mooney et al., 2010), at this time-point in rats, the majority of cells within the tissue capsule no longer express haemopoietic markers (CD45 or CD68) and most express myofibroblast markers α-SM actin and SM22 (Le et al., 2010).

The essential role of macrophages in the peritoneal foreign body response was confirmed by experiments using MacGreen mice in which macrophage depletion with clodronate liposomes almost completely abrogated tissue capsule development (Mooney et al., 2010). We further showed that as the tissue capsule developed around foreign body implants in the peritoneal cavity, a sub-population of $EGFP^+$ cells appeared that co-expressed the myofibroblast marker α-SM actin. The proportion of $EGFP^+$ α-SM $actin^+$ cells increased with time, reaching 51±1% of total cells (approx 80% of total α-SM $actin^+$ cells) at later stages of tissue development. The morphology of $EGFP^+$ α-SM $actin^+$ cells also changed from a rounded macrophage-like appearance to a more spindle-shaped myofibroblastic phenotype, thus providing evidence that cells of myeloid origin can transdifferentiate to myofibroblasts (Mooney et al., 2010). These results are in agreement with those of Jabs et al (2005) who demonstrated that labelled peripheral blood mononuclear cells contributed to tissue capsule formation and that from day 14 onwards, a proportion of α-SM actin-expressing spindle-shaped cells co-expressed macrophage markers (ED1/ED2).

Macrophage transdifferentiation has been documented in a number of other settings. Cultured peritoneal macrophages from mice chronically infected with *Schistosoma manosi* exhibited fibroblast-like characteristics and co-expressed fibroblast (pro-collagen) and macrophage (mac-1/mac-2) markers (Godoy et al., 1989; Bertrand et al., 1992) while monocyte-derived macrophages in infarcted myocardium have been reported to differentiate to myofibroblasts (Fujita et al., 2007). In response to transforming growth factor (TGF)-β, cultured peritoneal-derived macrophages have also been shown to transdifferentiate into smooth muscle-like cells/myofibroblasts, expressing smooth muscle/myofibroblast markers such as calponin and α-SM actin and down-regulating expression of the macrophage marker CD11b (Ninomiya et al., 2006).

Although there is now convincing evidence for the direct involvement of macrophages as cellular progenitors of fibrotic tissue, other cellular sources of peritoneal myofibroblasts are also possible. Vranken et al (2008) identified stem/progenitor cells expressing Sca-1, c-kit, CD34 and CD271 as major contributors to the early foreign body response to bovine pericardium patches implanted in the peritoneal cavity. Importantly these latter cells were shown to have the potential to differentiate to a number of lineages, including myofibroblastic. More recently this same group has suggested that fibrocytes ($CD68^+CD34^+$), rather than macrophages ($CD68^+$ $CD34^-$) are able to differentiate to myofibroblasts (Mesure et al., 2010).

Macrophages also have indirect (paracrine) roles in the fibrotic response to foreign material, releasing cytokines, growth factors, other inflammatory mediators and matrix degrading enzymes to modulate the inflammatory response and regulate tissue repair (Xia & Triffitt, 2006). In serosal wound healing and fibrosis, macrophages have been implicated to play a supporting role via the release of cytokines/growth factors which stimulate mesothelial cell proliferation (Mutsaers et al., 2002) and fibrogenic processes such as ECM synthesis (Sakai et al., 2006). Macrophages also play a key role in angiogenesis and tissue repair, releasing matrix metalloproteinases and angiogenic growth factors (Murdoch et al., 2008) and co-operating with progenitor cells (Anghelina et al., 2006).

5. What regulates tissue capsule development and myofibroblast differentiation?

In order to identify key transcriptional events associated with development of the non-adhered, avascular myofibroblast-rich tissue encapsulating foreign objects implanted in the peritoneal cavity, our laboratory performed microarray expression profiling of tissue from different stages of capsule development in a rat model (Le et al., 2010). Consistent with changes in cellular composition, the data showed a change in gene expression over time from inflammatory, particularly myeloid cell-associated (including genes for CD14, CSF-1 and its receptor, CSF-1R) at the early stages of capsule formation, to myofibroblast-related (including SM-22 and fibulin) at later stages. The temporal changes in gene expression included the early up-regulation of genes for inflammatory mediators and chemokines (such as monocyte chemoattractant protein (MCP)-1, monocyte inflammatory protein (MIP-1α) and its receptor CCR1, and stromal-derived factor (SDF)-1) to attract inflammatory cells (mainly macrophages) to the foreign object, as well as altered expression of adhesion molecules associated with inflammatory responses and (later) tissue morphogenesis.

Also identified were growth factors and cytokines (including platelet-derived growth factor (PDGF) and TGF-β) known to be released by macrophages at the onset of the foreign body response (Luttikhuizen et al., 2006), as well as ECM proteins (collagens I and 3, biglycan, decorin, syndecans-1 and –2) and enzymes associated with fibrosis and tissue remodelling (matrix metalloproteinases MMP-2 and -9) and their inhibitors (plasminogen activator inhibitor (PAI)-1 and tissue inhibitor of metalloproteinase (TIMP)-1). In addition to its role as a potent mitogenic and chemotactic agent for myofibroblast progenitors (Lindahl & Betsholtz, 1998), PDGF-BB is associated with the early stages of myofibroblast differentiation from progenitor cells (Oh et al., 1998). TGF-β is the principal mediator of myofibroblast differentiation in wound healing, inducing fibroblasts (and possibly other cell types) to differentiate into α-SM actin-expressing myofibroblasts with the capacity for contraction and ECM synthesis (Leask & Abraham, 2004). TGF-β signalling was significant throughout tissue development, as evidenced by the continued expression of its receptor (TGFβRII) and downstream signalling molecules (SMAD-1,-2,-4 and latent TGF-β binding protein (LTBP)-2), as well as up-regulated expression of TGF-β inducible genes including connective tissue growth factor (CTGF), insulin-like growth factor binding protein (IGFBP)-3, TIMP-1, PAI-1, decorin and collagen I subunits (Verrecchia et al., 2001, 2006). The biological relevance of the data was confirmed by cell culture studies which showed that PDGF-BB stimulated the proliferation of tissue capsule cells, while TGF-β_1 inhibited the response to serum mitogens but induced expression of α-SM actin (Zhang et al., unpublished data). Myofibroblast differentiation was further enhanced by a cocktail of PDGF, interleukin (IL)-13 and TGF-β. Moreover inhibition of TGF-β signaling, by either chemical inhibition of TGFβRI (ALK5) (with LY-364947; Sawyer et al., 2003) or siRNA inhibition of TGFβRII, reduced α-SM actin expression by these cells *in vitro* and inhibited tissue development *in vivo*, demonstrating the critical role of this growth factor in the peritoneal foreign body response (Chau et al., unpublished data).

Functional analysis of the gene array data identified *Immune Response* and *Immune System Development and Function* as significant during the early stages and *Connective Tissue and Development and Function* at later stages of tissue development. The importance of fibrotic signalling was corroborated by pathway analysis identifying '*Hepatic Fibrosis/Hepatic Stellate*

Cell Activation' as significantly up-regulated at days 14 and 21. Although peritoneal tissue capsules show no evidence of vascularisation, the gene expression data provides additional evidence of the potential of capsular cells for angiogenesis, with genes for angiopoietins-1 and -2, vascular endothelial growth factor (VEGF) and its receptors Flt-1 and Flk-1 up-regulated. Moreover, the identification of *Cardiovascular System Development and Function* and *Skeletal and Muscular System Development and Function* as significant at day 14 indicates that, although the tissue capsule does not develop these functions, cells within it may have the potential to differentiate further along multiple pathways. This finding provides a molecular basis for our demonstration that when transplanted into smooth muscle organs within the same animal, cells within the tissue differentiate further towards a smooth muscle phenotype (Campbell et al., 1999, 2008; Efendy et al., 2000). The identification of genes associated with other mesenchymal lineages such as endothelial, cardiac and skeletal muscle suggests the capacity to differentiate to these cell types, given the appropriate environmental conditions.

While this study provided information regarding global changes in gene expression associated with the tissue response to foreign body implantation, information regarding gene expression by individual cell types is also required. To this end, a recent study by Mesure and co-workers (2010) showed up-regulated expression of cytokines and inflammatory response genes in $CD68^+$ cells isolated from tissue 3 days after foreign body implantation; pathways related to the innate immune response (IL-1α, IL-1β, IL-6, IL-10 and tumour necrosis factor (TNF)-α), cell adhesion (ICAM-1, VCAM-1) and matrix remodelling (MMP-13) were identified. In vitro culture of these cells with fibrinogen showed a switch over time from inflammatory to wound healing macrophages, evidenced by over-expression of genes such as IL-13Rα IL4Rα and arginase 1, and up-regulation of TGF-β signalling. These results are in line with an earlier study by Garrigues et al (2005) who identified a small number of genes which are highly regulated in macrophages exposed to wear debris from components of joint replacement prostheses. These included early changes (30 mins to 8 hours) in genes associated with ECM remodelling and angiogenesis, and also chemokines (IL-6), cytokines (RANTES, MIP-1α) and their receptors (TNFR1, 2 and IL2αR); other inflammatory cytokines (IL-1β, TNF-α, TGFβ3, oncostatin M) and IL6R-α subunit were up-regulated slightly later (at 24 hours).

Examination of cytokine production by biomaterial-adherent macrophages similarly showed expression of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and MIP-1β) highest at early stages (day 3) while IL-10 expression increased later, suggesting a phenotypic switch over time from classically activated to alternatively activated macrophages (Anderson & Jones, 2007). This has been corroborated by a recent study in our laboratory which identified two major phases: an inflammatory phase characterised by high levels of expression of Th1/M1 cytokines (IL-1β and TNF-α) at day 2, and a fibrotic phase regulated by TGF-β signalling pathways (Jahnke et al., unpublished data). Early expression of chemokines MCP-1, MIP-1α, RANTES and GRO/KC highlighted the importance of recruitment of inflammatory cells to the foreign object.

6. Modification of the foreign body response

The identification of strategies to regulate the foreign body response has important implications both for tissue engineering and for the proper functioning of implanted

medical devices. *In vitro* studies have shown that although the foreign body response cannot be completely avoided, monocyte adhesion is influenced by surface chemistry of the biomaterial, the type and amount of adsorbed protein, and adhesion time (Shen & Horbett, 2001). Possibilities to modulate the response and the cellular content of resulting tissue also exist.

Attempts to reduce the fibrotic response to implanted medical devices have included the use of biocompatible coatings to mask the underlying material and reduce protein adsorption and cellular interaction. Coating materials tested include synthetic polymers such as poly(vinyl alcohol) (Galeska et al., 2005), poly(lactic acid) and poly(lactic co-glycolic) acid (Athanasiou et al., 1996). Naturally occurring materials such as chitosan (Borchard & Junginger, 2001), collagen (Geiger et al., 2003) and alginate (de Vos et al., 2002) have also been used, although these are frequently immunogenic and subject to natural variability in their macromolecular structure (Morais et al., 2010). They also allow better cell adhesion and therefore may be more suitable for tissue engineering applications requiring enhanced tissue production (Cheung et al., 2007). The physical attributes of the material may also be important, with both porous PLA (Koschwanez et al., 2008) and collagen (Ju et al., 2008) coatings shown to reduce fibrosis and/or promote blood vessel formation to enhance function and life-time of implantable glucose sensors.

Hydrogels composed of polar, uncharged, flexible materials such as poly (hydroxyethyl methacrylate) (PHEMA) or polyethylene glycol (PEG) form a hydrophilic interface between the underlying surface and the surrounding tissue, and allow analyte diffusion (Wisniewski & Reichert, 2000). PEG-based hydrogels have been shown to substantially reduce the immune response around biosensors implanted in rats (Quinn et al., 1997) while PHEMA coatings reduced clotting and protein adsorption to calcium monitors in dogs (McKinley et al., 1981). Phospholipid-containing materials designed to mimic the cell membrane have been shown to reduce adhesion of inflammatory cells and fibrous capsule formation around vascular devices (Goreish et al., 2004) while Abraham et al. (2005) showed that formulations incorporating PEG and phosphorylcholine into PHEMA-based hydrogels greatly reduced protein adsorption.

Alternatively, strategies may be directed towards augmentation of the foreign body response for tissue engineering. In our attempts to enhance the production of tissue for transplantation as autologous grafts for hollow smooth muscle organs, we tested the tissue response to peritoneal implantation of poly(lactic acid) tubular scaffolds with different layer-by-layer biomolecule coatings (as described by Croll et al., 2006). Immunohistochemical analysis of the resulting tissue showed that Matrigel-coated surfaces supported the strongest cellular response whereas multilayer coatings with elastin, collagen I, collagen III or chitosan outermost showed the lowest levels of cellular interaction. While differences in capsule thickness and growth characteristics were observed, all of the biomolecule coatings tested induced the peritoneal foreign body response, even in the presence of a non-adsorptive hyaluronic acid undercoat (Cao et al., 2008).

The variable ability of polymeric coatings to reduce acute and chronic inflammatory responses *in vivo* (Shen et al., 2002; Park & Bae, 2003) has led to investigation of anti-inflammatory drugs to inhibit the tissue response to biomaterials. The most commonly used drug has been dexamethasone which modulates macrophage behaviour and reduces the levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α (Joyce et al., 1997; Umland et al., 2002). Burgess and co-workers embedded dexamethasone-containing

PLGA microspheres in PVA hydrogels to create a 'smart' coating for glucose sensors which allowed rapid diffusion of analytes and slow release of dexamethasone (Hickey et al., 2002; Patil et al., 2004). Other anti-inflammatory strategies investigated include heparin-based coatings to reduce protein adsorption and leukocyte recruitment (Rele et al., 2005) and covalent conjugation of a superoxide dismutase mimetic to the surface of biomaterials, resulting in reduced neutrophil recruitment and inhibition of foreign body giant cell and fibrous tissue capsule formation (Udipi et al., 2000). However Jones (2007) has suggested that minimisation of the inflammatory response to implanted biomaterials may be counter-productive, and that a preferable strategy would be to design materials to direct the response towards reparative/wound healing. For example, it may be possible to tip the balance away from production of TGF-β1 (which promotes fibro-proliferation) towards TGFβ3 (which promotes tissue repair) (Ask et al., 2008). Indeed glucocorticocoid drugs have been shown to modulate the phenotype of infiltrating macrophages and lymphocytes (Peek et al., 2005; Mosser & Zhang, 2008) and could thus be used locally to regulate the cellular response.

By altering the cell populations recruited to the foreign body it may be possible to modify the inflammatory response to implanted foreign material, as well as the cellular nature of the subsequent tissue response. Given that chemokines regulate cell trafficking (Gerard & Rollins, 2001) and play a key role in the recruitment of inflammatory cells in the peritoneal foreign body response (Luttikhuizen et al., 2007), chemokines may be an important target for intervention. De Visscher et al. (2010) have shown that impregnation of bioprosthetic heart valves with SDF-1 and fibronectin modulated the cellular response to produce more biologically relevant tissue with properties very similar to native valves, whilst Thevenot et al. (2010) showed that delivery of SDF-1α to the site of biomaterial implantation increased the recruitment of host stem cells, and at the same time reduced the inflammatory response, such that the fibrotic response to scaffold implants was ameliorated. They suggested that enhanced recruitment of autologous stem cells can improve the tissue responses to biomaterial implants through modifying/bypassing inflammatory cell responses and stimulating stem cell participation in healing at the implant interface. Our preliminary experiments show that continuous infusion of AMD3100 (a specific antagonist of the SDF-1 receptor, CXCR4; Matthys et al., 2001) does not inhibit encapsulation of foreign material implanted in the peritoneal cavity, but alters the cellular composition of the encapsulating tissue (Le et al, unpublished data). Another important chemokine, MCP-1, is highly expressed at the early stages of the cellular response to foreign body implantation (Le et al., 2010), and has been implicated in the pathogenesis of progressive fibrosis in lungs (Moore et al., 2001) and kidney (Kitagawa et al., 2004). Via its receptor CCR2, MCP-1 plays an important role in the recruitment of inflammatory monocyte subsets from the bone marrow into injured tissues (Geissmann et al., 2003; Karlmark et al., 2009). However Kyriakides et al. (2004) demonstrated that the lack of MCP-1 resulted in reduced foreign body giant cell formation, but did not affect either the recruitment/migration of macrophages to the site of biomaterial implantation or capsule formation.

Biomaterials may also be used to deliver anti-fibrotic drugs/inhibitors. As mentioned above, we have shown that inhibition of TGF-β signalling either by siRNA knockdown of TGFβRII or chemical inhibition of TGFβRII (ALK5) inhibits myofibroblast differentiation in vitro and peritoneal tissue capsule formation in vivo (Chau et al, unpublished data). However in light of the pleiotropic roles of TGF-β, a more suitable target for selective intervention may be the

downstream effector, connective tissue growth factor (CTGF) which is responsible for many of the pro-fibrogenic effects of TGF-β (Ward et al., 2008; Brigstock, 2009).
Conversely, chemokines/growth factors may be incorporated into biomaterials to promote tissue production for replacement/repair. For example, polylactic/glycolic acid scaffolds (as described by Cao et al., 2006) stabilise and prolong the half-life of growth factors, and provide a means for localised release of the growth factor at a controlled dose and rate of delivery over a prolonged period (Richardson et al., 2001). Chemokines and growth factors could be incorporated into different layers, then released sequentially to first recruit cells to the scaffold, then promote the proliferation of adherent cells, and finally induce their differentiation to produce mature tissue.

7. Conclusion

The ability to regulate the fibrotic response to implanted materials has important implications for bioengineering, both to control the deleterious response to implanted medical devices and to enhance the production of tissue for organ repair. Myofibroblasts are critical for appropriate wound healing and tissue repair, but are also responsible for fibrosis. Hence understanding the origins of cells involved in the development of myofibroblast-rich tissue, and identification of the mechanisms regulating their (trans)differentiation and biology, is the key to successful bioengineering strategies.
Our research into the peritoneal foreign body response questions the traditional notion of distinct terminally differentiated cell types with specific functions. The results demonstrate a developmental continuum from monocyte (or granulocyte) through macrophage to myofibroblast, and potentially smooth muscle and/or other cell types. Given that cellular plasticity is a hallmark of the myeloid lineage (Hume, 2008), these findings extend the prevailing concepts of adult cell fate. We propose that, at least for some cell lineages, cellular identity is more fluid than previously recognised. Thus within its life-time, a single cell has the capacity to adopt a range of phenotypes and functions according to physiological needs and local regulatory milieu. While research to date has focussed on strategies to minimise/inhibit the inflammatory response to biomaterials, a preferable strategy may be to direct the response towards immune tolerance and tissue regeneration.

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Tissue Engineering may offer new treatment alternatives for organ replacement or repair deteriorated organs. Among the clinical applications of Tissue Engineering are the production of artificial skin for burn patients, tissue engineered trachea, cartilage for knee-replacement procedures, urinary bladder replacement, urethra substitutes and cellular therapies for the treatment of urinary incontinence. The Tissue Engineering approach has major advantages over traditional organ transplantation and circumvents the problem of organ shortage. Tissues reconstructed from readily available biopsy material induce only minimal or no immunogenicity when reimplanted in the patient. This book is aimed at anyone interested in the application of Tissue Engineering in different organ systems. It offers insights into a wide variety of strategies applying the principles of Tissue Engineering to tissue and organ regeneration.

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