Chapter 2
Stromal Cell Responses in Infection

Paul M. Kaye

Abstract Stromal cells and the immune functions that they regulate underpin multiple aspects of host defence, but the study of stromal cells as targets of infection and as regulators of anti-infective immunity is in its infancy and still limited to a few well-worked examples. In this review, the role of stromal cells at each sequential stage of infection is discussed, with examples drawn from across the spectrum of infectious agents, from prions to the parasitic helminths. Gaps in knowledge are identified, the challenges in studying stromal cell biology in the context of infection are highlighted, and the potential for stromal cell-targeted therapeutics is briefly discussed.

Keywords Stromal infection · Innate immunity · TLOs · Stromal architecture · Stromal APCs · Inflammation resolution

2.1 Introduction

The pathogenesis of infectious disease is complex and involves a myriad of processes, some but not all related to core immune mechanisms, most of which in one form or another are underpinned by features of stromal cell biology. Stromal cells provide the tissue architecture at the primary interface with infectious agents (e.g. the skin or mucosa), act as a potential cellular target for infection, provide the framework for the compartmentalized functions of lymphoid tissue and immune response induction and generate and maintain the vascular environment that allows for effector cell trafficking to the sites of infection. At the end of infection, stromal cells play a role in resolution of immune-mediated pathology and the return to homoeostasis. Details of many of these functions of stromal cells during development, under homoeostatic conditions and during cancer are described in

P. M. Kaye (✉)
Centre for Immunology and Infection, Department of Biology and Hull York Medical School, University of York, York, UK
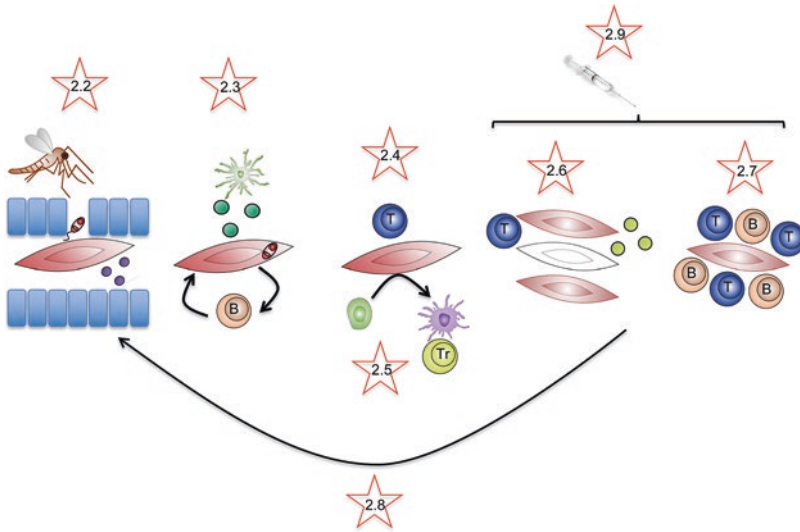e-mail: paul.kaye@york.ac.uk

Fig. 2.1 The temporal role of stromal cells in regulating immunity to infection. Schematic shows a stylized time course depicting the events from initial pathogen contact through to disease resolution that may be influenced by stromal cell interactions and functions. For examples of stromal cell interactions with specific pathogens at each stage (numbered stars), see main text

detail elsewhere in this volume. Here, the focus will be on providing key exemplars of how stromal cells interact, directly or indirectly, with pathogens and help to orchestrate subsequent inflammatory and immune responses that ultimately lead either to pathogen elimination or the establishment of a chronic persistent infection. The broader role of stromal cells in the resolution of infection-associated pathology is also discussed, although to date there are few studies addressing this important aspect of infection biology. For the sake of brevity, discussion regarding stromal cell interactions with pathogens associated with the development of cancer (e.g. Epstein-Barr Virus) has been omitted (Fig. 2.1).

2.2 Initiation of Infection: Stromal Cells as Targets for Adhesion and Infection

For successful infection to begin, pathogens require means to adhere to and/or penetrate external barriers. For mucosal pathogens, epithelial cells represent a major site of pathogen attachment at mucosal surfaces, and an intact epithelium provides a barrier to direct interaction between these infectious agents and underlying mesenchymal stromal cells. The role of crosstalk between epithelial cells and stromal cells, serving as an integral part of the signaling required for epithelial barrier function and maintenance, is well documented, notably in the female reproductive tract and mammary gland [1, 2]. This establishes a paradigm likely to be operating at

most epithelial sites and suggests that any disruption to this functional unit may occur through either epithelial or stromal cell changes.

Some mucosal pathogens such as *Entamoeba histolytica* [3] are professional tissue invaders and use a variety of molecular and cellular strategies to penetrate deep into the mucosa and submucosa; yet little attention has been paid to the consequences of such local tissue trauma for stromal cell function. Gastrointestinal worms have a variety of ways to interact with and manipulate the mucosal epithelium and otherwise disrupt local immunity [4, 5]; however, the direct action of helminth-derived molecules on intestinal stromal cells has not been reported in any detail.

Many of the major pathogens of man are transmitted via breaks in skin barrier that occur during blood feeding by their arthropod vector. For these pathogens, there may be more direct and immediate access to tissue stromal cells, and the tropism of intracellular pathogens to stromal cells after epithelial barrier breach provides an opportunity for their establishment and long-term survival. In addition to facilitating access to stromal cells, the tissue trauma caused by the bite of haematophagous insects may also directly trigger stromal cell release of alarmins (see below) [6]. In the case of the intracellular parasites, the reduced microbicidal capacity of stromal cells compared to myeloid cells may provide a driver for this behaviour. For example, the parasitic protozoan *Trypanosoma cruzi* invades the skin and oral mucosa in a process of contaminative transmission, with infectious metacyclic parasites being deposited in the faeces of feeding triatomine bugs. *T. cruzi* has a broad host cell range, making use of a plethora of attachment molecules and active processes to invade stromal cells in a process of triggered phagocytosis [7]. Other vector-borne parasites such as *Leishmania*, whilst historically regarded as having a more limited host cell range, have also been noted as intracellular parasites of stromal cells at chronic stages of infection [8, 9]. It is not clear whether stromal cell infection also occurs early after infection and has hitherto gone unrecognized.

In experimental models of infection, stromal cell tropism is also noted and may illustrate how tropism may be both cell- and tissue-specific in nature. For example, after intraperitoneal murine cytomegalovirus (MCMV) infection, ERTR7+ marginal zone reticular cells represent the major target for infection within the spleen, with subsequent viral spread to red pulp fibroblasts. In contrast, in the lymph node primary infection occurs within CD169+ subcapsular sinus macrophages [10].

These various studies also raise an important question regarding the temporal regulation of adhesion and/or pathogen selective receptors on stromal cells (e.g. by mediators involved in inflammation) and whether this may also contribute to the patterns of cellular tropism that are observed. For example, in the case of corneal infection with HSV, the major viral receptor nectin-1 is initially absent from stromal cells, but expression is induced early during inflammation allowing increased viral host cell range [11, 12]. Further studies in a variety of infection models to address the role of direct stromal cell infection at different stages of the infection process would clearly help in delineating the importance of such interactions to disease progression and pathogen life cycle maintenance.

HIV infection provides an interesting and relevant example of how stromal cells can both be target for infection and regulator of infection in other cells. HIV infects follicular dendritic cells (FDC), which provide a reservoir for viral infection of CD4+ T cells and macrophages [13–15], but in addition, these infected FDCs provide TNF-dependent augmentation of HIV transcription and viral replication in CD4+ T cells [16].

Finally, to fully define pathogen cellular tropism, it may be necessary to consider the potential for lineage transformation. At least one intracellular pathogen has been shown to induce epithelial-to-mesenchymal transition (EMT). The *cag* pathogenicity island of *Helicobacter pylori* encodes a type 4 secretion system that delivers bacterial effectors into the cytosol of gastric epithelial cells and induces EMT [17]. Whether this can be induced by other intracellular pathogens remains to be determined. Another instance where lineage boundaries become blurred is the case of the fibrocyte, which shares markers of haematopoietic cells and fibroblasts [18]. Recently, the capacity of human and murine blood fibrocytes to support internalization of promastigotes of *Leishmania amazonensis* was reported, along with the capacity of these cells to support intracellular transformation to amastigotes [19]. Strikingly, fibrocytes produced high levels of NO and cleared parasites within a few days of infection, suggesting that transient waves of infection within fibrocytes in vivo could go unnoticed. Furthermore, a variety of *Leishmania* species have been shown to infect adipose-derived mesenchymal stem cells in vitro [20], though whether this alters stem cell function and differentiation capacity has yet to be determined. It seems likely that at least some intracellular pathogens will be found to have the capacity to affect the pluripotency of stem cells, but this remains an area to be explored experimentally.

2.3   Early Inflammation: Stromal Cells as Contributors to Innate Immunity

Cooperation between haematopoietic and stromal cells can play an important role in initiating inflammation. For example, TLR4 expression on stromal cells is required for optimal resistance against uropathogenic *E. coli* but is not sufficient for induction of inflammation in the absence of TLR4 expression on haematopoietic cells [21]. Protection in a lethal model of vesicular stomatitis virus (VSV) infection required intact TLR and retinoic acid-inducible gene I-like helicase (RLH) signaling in both radioresistant stromal cells and haematopoietic cells [22]. Likewise, effective immunity in a model of oropharyngeal candidiasis required expression of the NLRC4 inflammasome in radioresistant stromal cells, working cooperatively with NLRP3 inflammasome [23].

Recent studies in the well-established MCMV infection model have also provided insight into how stromal cells can play a direct role in innate immunity. Type I interferons are required for the early control of MCMV replication in the mouse spleen, and various studies have indicated that both plasmacytoid and conventional dendritic cells (DCs) play temporally discrete roles in producing the bulk of type I interferon detectable between 36 and 48 h postinfection. However, this wave of type

I interferon is preceded (2 h postinfection) by a burst of type I interferon derived from LTβR-expressing splenic marginal zone reticular cells, acting in concert with LTαβ-producing B cells [24, 25].

Alarmins represent a constitutively available group of evolutionarily diverse molecules that normally have important intracellular roles but which can be released into the extracellular environment through tissue injury or inflammatory signaling cellular roles during regulation of innate immunity and may be triggered directly by tissue damage or indirectly through the production of other early mediators of inflammation such as IL-17. Alarmins include IL-33, various S100 molecules, HMGB1 and thymic stromal lymphopoietin (TSLP) [26, 27]. The contribution of stromal cells to the production and/or regulation of alarmins in the context of epithelial cell injury during infection is, however, poorly understood.

Some of the aforementioned papers, however, highlight a conspicuous difficulty in the field of stromal cell biology: assignment of the term "stromal" to cells that are radioresistant in radiation bone marrow chimeras. Whilst this experimental approach can identify, but not distinguish between, properties attributable to radioresistant mesenchyme-derived stromal cells and epithelial cells, the recent identification of radioresistant resident tissue macrophages of yolk sac origin [28–30] introduces some significant question marks over previous attribution of cell function. The ability to generate mouse strains for lineage tracing and for selective stromal cell-targeted gene ablation (e.g. [31]) is an important step towards clarifying the function of stromal cells throughout the infection process.

2.4 Induction of Acquired Immunity: Stromal Cells as APC During Infectious Disease

The notion that antigen presentation within lymphoid tissues is restricted to haematopoietic cells has been over-turned by a number of recent studies that indicate that stromal cells have all the machinery necessary for both MHCI [32, 33] and MHCII-dependent antigen presentation [34] and in addition can acquire and functionally express MHCII-peptide complexes derived from DCs [35]. Under homoeostatic conditions, this imparts an ability to effect CD8+ T cell deletion to self-antigens and regulate the extent of CD4+ T cell priming, either directly by inducing anergy [35] or indirectly by maintaining the pool of CD4+ Tregs [34]. The extent to which pathogen-derived antigens are presented in this way by stromal cells within the lymphoid tissue microenvironment is as yet unknown but clearly warrants further investigation given the potential for this route of antigen presentation to modify the quantity (and perhaps quality) of the response to infection. Whether stromal cells outside lymphoid tissue also are endowed with these properties will be important to address, as will be the question of whether stromal cell antigen presenting function "matures" through infection, in an equivalent manner to that seen in the haematopoietic lineage. In this context, it is interesting to note that inflammation, including that driven by infection, can lead to local tissue fibroblasts recapitulating the ontogeny of lymphoid tissue fibroblasts, expressing the canonical lymph node stromal

marker podoplanin (gp38) [36]. Whether these cells acquire all functions associated with their lymphoid tissue resident counterparts remains to be determined, and illustrates an experimental setting where transcriptomic analysis of stromal cells might be particularly helpful.

2.5   Maintaining the Balance: Stromal Cells and Immune Regulation

As indicated above, new evidence indicates that lymph node stromal cells can directly engage with T cells via MHCI and MHCII restricted antigen presentation, and that the primary purpose of these interactions under homeostatic conditions appears to be the induction of one or other mechanism of self-tolerance. To date, however, most attention has been focused on how stromal cells induce a regulatory environment and thus influence T cell activation indirectly rather than directly. Early studies in vitro demonstrated the capacity of stromal cell lines to drive HSPC into a programme of myelopoiesis, often generating novel subsets of dendritic like cells [37–39]. In a model of *Leishmania donovani* infection, it was shown that ex vivo isolated stromal cells were able to induce lin⁻c-kit⁺ progenitors to differentiate to a greater extent that stromal cells isolated from uninfected mice. Furthermore, the resulting CD11c^{lo} CD45RB$^+$ IL-10-producing DCs had potent regulatory properties (defined in vitro by suppression of T cell proliferation to antigen presented by conventional CD11c DC and in vivo by the induction of antigen-specific tolerance) [9]. Subsequently, it was demonstrated that infection-associated inflammation enhanced the function of this splenic red pulp stromal haematopoietic niche, principally through aberrant expression of CCL8 [40].

A challenge for studying stromal cell biology in an infection model where stromal cells themselves can be infected, albeit at variable frequency, is to distinguish whether any changes in stromal cell function are directly attributable to intracellular parasitism (e.g. mediated via parasite-induced host cell intrinsic changes in signaling pathways) or whether they reflect the action of cytokines and or other factors operating in trans in a complex inflammatory "soup". Importantly in the latter study [40], stromal cell lines were used to show that CCL8 expression was directly induced in stromal cell lines in vitro by infection with *L. donovani* and that in vivo, CCL8$^+$ ERTR-7$^+$ stromal cells also contained parasites. These data do not however rule out trans-acting factors as contributors to the in vivo response. Indeed, as endothelial cells and fibroblasts isolated from various tissues, with or without inflammatory stress, have been shown to induce regulatory myeloid cells capable of inhibiting T cell responses [41–45] and in one case to block virus-mediated activation of pDC [46], it is likely haematopoietic support is a generic tunable property of stromal cells that helps maintain immune balance.

Stromal cells have been less well studied in the context of helminth infections and immune regulation. B cells have been shown to play a role in immune regulation in some chronic infections. In the case of *Schistosoma mansoni* infection, regulatory B cell development has been linked to the production of BAFF, a cytokine produced

by DC and stromal cells in response to helminth antigens [47]. Surprisingly, stromal cell modifications have also been implicated in the onward transmission of this parasite. *S. mansoni* egg excretion is essential for completion of the life cycle, and this is facilitated by entry of eggs into Peyer's patches, which respond with extensive remodeling of their stromal elements [48].

In summary, whilst it is tempting to "hand-wave" by saying that stromal cells are almost certain to have a role in the overall generation of the changing immune environment during infection, through participation in the control of lymphocyte and dendritic cell functions or through their contribution to the cytokine environment, only carefully designed and executed studies using stromal cell specific targeting of key immune mediators will provide the answer to the question of how important stromal cell responses are relative to those of other cells in driving the ultimate phenotype – pathogen elimination or persistence of infection.

2.6 Perpetuating Chronic Infection: Breakdown of Stromal Cell Architecture

As detailed elsewhere within this volume, stromal cells play a central role in the development and maintenance of lymphoid tissue architecture. On the assumption that immune architecture is therefore integral to the efficiency of the immune system, it is perhaps not surprising that many studies of disease, including infectious disease, have noted changes in lymphoid tissue architecture and associated these with dysregulation of immunity.

Examination of the lymph nodes of patients with progressive HIV infection demonstrated marked degenerative changes to germinal centres, including the depletion of the FDC network, a process termed follicle lysis [49, 50]. Of note, a study in SIV-infected macaques demonstrated that although FDCs were also greatly reduced in number in this model infection, residual FDCs appeared to make more functionally productive interactions with B cells [51]. This study serves as a reminder that pathology-associated loss of cell number should not be equated directly with loss of function. Similar structural changes to the FDC network have also been observed in non-viral infection models, including chronic visceral leishmaniasis. Here, FDC loss was determined both by immunohistochemistry and by lack of immune complex trapping within GCs [52]. Strikingly, heavily parasitized macrophages became abundant within these GCs, resembling the tingible body macrophages described in HIV infection [49].

The demonstration that a distinct population of podoplanin+ fibroblastic reticular cells was present within the T cell zone of lymphoid tissues focused attention on how this stromal cell subset was altered in a variety of infection models. In chronic HIV infection, fibrosis of lymphoid tissue becomes apparent, and this results in loss of integrity of the FRC network. Importantly, the extent of loss of FRCs and collagen deposition are predictors of the ability of highly active antiretroviral therapy (HAART) to restore T cell count. Furthermore, HAART is most effective at restoring FRC networks when given early during disease [53, 54].

FRCs are also lost during infection with *Leishmania donovani* in mice [55]. As expected, FRC deficiency was also characterized by a loss of constitutive CCL21 and CCL19 production in the spleen of infected mice and by alterations in DC and T cell traffic. Although DC migration from the marginal zone into the T cell zone was impaired in infected mice, this was not the direct result of loss of FRCs. By adoptive transfer, it was shown that the residual FRCs and CCL21-expressing endothelium were sufficient to allow migration of DC isolated from naïve mice, and whereas conversely DCs from infected mice failed to migrate even in naïve hosts. Hence in this case, loss of CCR7 expression by DCs in infected mice, which was in turn regulated in a TNF and IL-10-dependent manner, appeared to play a more dominant role in affecting DC-T cell interactions than the loss of stromal architecture per se. Of interest in this regard, computational models have been developed to assess the impact of changes in FRC network density and inter-connectivity in regulating cellular encounters between T cells and DC [56].

Unlike the situation in chronic HIV and visceral leishmaniasis, experimental viral infections provide examples of situations where extreme but transient pathology occurs. In LCMV infection, splenomegaly is transient, peaking during the first week of infection but subsiding to normal range within 10 days. Loss of FRCs accompanies splenomegaly, as does inability to respond to challenge with exogenous antigens, but the FRC network recovers remarkably quickly as infection is cleared. Restoration of this architecture is dependent upon the presence of RORγ⁺ lymphoid tissue inducer cells and LTαβ signaling, suggesting that "repair" of lymphoid tissue architecture recapitulates processes that occur during lymphoid tissue development [57]. During MCMV, disruption of lymphoid stroma appears restricted to the FRCs, which show similar alterations in gp38 staining pattern and changes in CCL21 expression as observed in visceral leishmaniasis and LCMV infection. B zone stromal cells, however, appear not to be significantly affected during this infection, as judged by maintenance of CXCL13 [58].

In addition to stromal cell changes, other microarchitectural changes often accompany splenomegaly, notably loss or displacement of "stromal" macrophages within the marginal zone. Mice infected with *L. donovani* [59], *Plasmodium chabaudi* [60] and MCMV [58] all show loss of SIGNR1⁺ marginal zone and CD169⁺ marginal metallophils to a greater of lesser extent. Collectively, these data illustrate that there is a degree of commonality in the structural changes seen irrespective of infectious agent. However, the process of remodeling may be driven by quite independent mechanisms. For example, in LCMV infection, antiviral CD8⁺ T cells destroy FRCs [57]; in *P. chabaudi* infection, CD8⁺ T cells selectively kill CD169⁺ marginal metallophils through a perforin and Fas-dependent pathway [60]; and during *L. donovani* infection, SIGNR1⁺ marginal zone macrophages are lost in a TNF-dependent manner [59]. The precise impact that can be attributed to changes in secondary lymphoid tissue, in terms of immunocompetence, may not be possible to discern from simple single infection models such as those described above and may require adaptation of various co-infection models to become fully apparent.

The chronicity and extent of *Leishmania donovani*-induced splenomegaly also provide a context in which pathologic angiogenesis occurs to an exaggerated extent. Vascular remodeling in this disease requires the coordinated action of distinct myeloid

cell populations, working in a compartment-specific manner. Thus, inflammatory monocytes regulated the expansion of the red pulp vasculature [61], whereas a population of "resident" macrophages, which were found bordering the denuded marginal zone, play a role in inducing neo-angiogenesis in the white pulp. Of note, this localized angiogenesis is controlled by the aberrant expression of the neurotrophin Bndf and its receptor Ntrk2 (Trkb) on macrophages and endothelial cells, respectively [62].

2.7 Perpetuating the Response: Ectopic Lymphoid Structures

Chronic inflammation is often associated with the generation of ectopic or tertiary lymphoid tissue, a topic summarized elsewhere in this volume. Not surprisingly, therefore, infections may also give rise to these structures, although their significance for disease progression is less well understood than in other settings.

Perhaps best characterized in animal models is the development of ectopic lymphoid structures associated with salivary gland inoculation of MCMV [63] and in the bronchus-associated tertiary lymphoid tissue associated with influenza virus infection [64]. A recent comparative study of *M. tuberculosis* infection in humans, in non-human primates and in mouse models provides perhaps the best characterized evaluation of the role of ectopic lymphoid tissue in disease progression [65]. Of note, whereas tuberculosis (TB) granulomas in patients and non-human primates with latent disease had associated ectopic lymphoid tissue, this was not the case for granulomas in patient or animals with active TB, suggesting a role for these structures in immune control. The finding of ectopic lymphoid tissue associated with the TB granuloma may be a special case, associated with either the chronicity of infection or the inherent adjuvant properties and/or immunogenicity of this pathogen. In other granulomatous diseases, e.g. experimental visceral leishmaniasis [66], granulomas do not acquire this feature.

2.8 Closure: Stromal Cells and the Resolution of Inflammation

Pathogen clearance ultimately leads to a reversal of most of the associated tissue pathology, through an active process of resolution. Recent evidence suggests that resolution is as complex a process as the generation of immunity and immunopathology, involving a plethora of distinct signals often mediated through shifts in metabolic profile of the tissue. As stromal cells are regarded as the key drivers for chronic inflammation [67], it goes without saying that resolution must bring about changes to the stromal compartment and that stromal cells may indeed drive this process, for example, through consumption of survival signals or the active production of resolution-promoting molecules [68].

The role of pro-resolution inflammatory mediators in the resolution of inflammation during infectious disease, including the role of lipoxins in models of *Toxoplasma gondii*, *Trypanosoma cruzi* and *Plasmodium berghei* infections, has recently been reviewed [69], whereas the role of resolvins has been most clearly illustrated in the control of herpes simplex virus infection [70]. Nevertheless, in the context of infectious disease, this area of stromal cell biology still offers huge potential not only for uncovering new regulatory pathways per se but for the identification of novel approaches to hasten, when appropriate, the resolution of infection-associated inflammation in the clinic.

2.9   Host-Directed Therapy: Stromal-Targeted Therapeutics for Infectious Disease

The development of immunotherapies targeting stromal cells is also described in detail elsewhere in this volume. Studies in infectious disease have provided three main examples to date where stromal cell-targeted immunotherapy might have an impact on the disease outcome. In the case of HIV, there is a good correlation between the extent of FRC disruption, collagen deposition and the ability of HAART to restore CD4^{+} Tcell count in patients [54, 71]. In experimental MCMV infection, targeting the LTβR with an agonistic mAb was able to restore otherwise defective CCL21 production and to improve homing of T cells into the T zone of MCMV-infected mice [58]. Finally, in an experimental model of visceral leishmaniasis, therapeutic administration of the broad-spectrum tyrosine kinase inhibitor sunitinib had no direct therapeutic benefit but was able to restore FRC and FDC networks. When used in a sequential therapy regimen with conventional antimonial-based chemotherapy, a marked dose-sparing effect was observed that correlated with enhanced T cell effector function [62]. Given the narrow therapeutic window for many anti-parasite drugs and the common occurrence of lymphadenopathy and/or splenomegaly, these data suggest that immunotherapies targeted at restoring lymphoid tissue architecture or minimizing collateral damage due to fibrosis may have a unique place in the future development of anti-infective therapies.

2.10   Concluding Remarks

Although there has been an explosion in the study of stromal cells in recent years, an appreciation of their role in infectious disease pathogenesis is still in its infancy. Tools are now becoming available to fate map stromal cells under conditions of ongoing infection, conditionally deplete or modify their function and explore their characteristics at a global level, suggesting a rich harvest awaits those who choose to enter this field, bringing with them the diversity of pathogens that have contributed so much in the past in terms of understanding the biology of haematopoietic cells. Ultimately, the ability to study stromal cell populations in human infectious disease

will become more tractable, and perhaps in the not too distant future, manipulating stromal cell function to combat infectious disease may become a clinical reality.

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