The Carcinoma-Associated Fibroblast Expressing Fibroblast Activation Protein and Escape from Immune Surveillance

Douglas T. Fearon

Abstract

The fibroblastic element of the tumor microenvironment has been of great interest to cancer biologists but less so to cancer immunologists. Yet, the sharing of a common mesenchymal cell type in the stroma of tumors and at sites of chronic inflammatory lesions, some of which have an autoimmune basis, has been a strong hint that this cellular component of the tumor microenvironment may have an immunologic function. Recent studies have confirmed this possibility. These fibroblast-like cells, which are termed carcinoma-associated fibroblasts (CAF), can be identified by their expression of the membrane protein, fibroblast activation protein-α (FAP). The conditional depletion of the FAP⁺ CAF permits immune control not only of an artificial, transplanted tumor, but also of an autochthonous model of pancreatic ductal adenocarcinoma (PDA) that replicates the molecular, histologic, clinical, and immunologic characteristics of the human disease. Immune suppression by the FAP⁺ CAF is mediated by CXCL12, the chemokine that binds to cancer cells and excludes T cells by a mechanism that depends on signaling by the CXCL12 receptor CXCR4. Inhibition of CXCR4 leads to the elimination of cancer cells by enabling the rapid, intratumoral accumulation of preexisting, PDA-specific CD8⁺ T cells, and reveals the antitumor efficacy of the T-cell checkpoint antagonist anti–PD-L1. Recent studies have also shown that the FAP⁺ CAF is related to FAP-expressing stromal cells of normal tissues, demonstrating that cancers recruit a member of an essential stromal cell lineage that is involved not only in wound repair but also in normal tissue homeostasis. These findings extend the concept introduced by cancer biologists that the fibroblastic component of tumors has a critical role in the adaptation of the cancer to the host. Cancer Immunol Res; 2(3); 187–93. ©2014 AACR.

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Learning Objectives

Fibroblast activation protein-α (FAP) is a membrane glycoprotein expressed on cells in the tumor stroma and in inflamed tissues during wound healing. In adipose tissue, skeletal muscle, and the pancreas, FAP⁺ stromal cells have essential homeostatic functions. The fibroblastic element of the tumor microenvironment has long been implicated in cancer development, and recent studies have shown that FAP⁺ carcinoma-associated fibroblasts (CAF) have immune-suppressive function. An understanding of how FAP⁺ CAFs mediate immune suppression will enhance the effectiveness of immunotherapy in cancer treatment. Upon completion of this activity, the participant should gain a basic knowledge of the contribution of FAP⁺ stromal cells to tumor immune escape.

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Background and Rationale

Tumor immunotherapy has entered a phase of rapid development with a shift in emphasis away from vaccination studies to a focus on various approaches to modifying the functions of T cells. The clinical efficacy of adoptive T-cell therapy with ex vivo expanded tumor-infiltrating T cells has been enhanced by the introduction of chimeric antigen receptors (CAR) into these cells. These recombinant CARs have defined antigenic specificities and improved signaling capabilities, but their
therapeutic efficacy has thus far been limited mainly to certain hematologic malignancies (1), suggesting that the microenvironments of solid tumors may have unique impediments to the functions of effector T cells. In support of this notion are the encouraging results with neutralizing antibodies to "T-cell checkpoints." Treatment with three checkpoint antagonists, anti-cytotoxic T lymphocyte antigen-4 (anti–CTLA-4; ref. 2), anti-programmed death-receptor 1 (anti–PD-1; ref. 3), and anti-PD ligand-1 (anti–PD-L1; ref. 4), has induced striking responses in subsets of patients with a range of solid tumors. An especially notable characteristic of these responses is their durability (5), which contrasts with the relatively limited duration of responses to "targeted" cancer therapies that interfere with specific signaling pathways mediating the carcinogenesis process. The lasting response to immunologic interventions may be a consequence of the potential of the immune system to recognize multiple antigenic targets in cancer cells, thus diminishing the likelihood that tumor cells will escape immune control. Interestingly, this hopeful, long-term outcome of immunotherapy was not predicted by the "cancer immunoeediting" hypothesis, which is predicated on the assumption that the host immune response rapidly selects for cancer cells that are not immunogenic, thereby enabling cancer to escape immune control (6).

The next phase in the development of cancer immunotherapy, however, must achieve an understanding of why T-cell checkpoint antagonists are ineffective in the majority of cancer patients. Even among the cancer types that do respond to anti–CTLA-4, anti–PD-1, or anti–PD-L1, such as melanoma, non–small cell lung cancer, and renal cell cancer, only 10% to 30% of the patients actually demonstrate objective control of tumor growth. Moreover, few patients with colorectal, pancreatic, ovarian, or prostatic cancer have been reported to benefit from treatment with T-cell checkpoint antagonists. Do they not respond because their immune systems do not recognize antigens associated with cancer cells, or because of the occurrence of another type of immune suppression? In melanoma, there is evidence both for (7) and against lack of spontaneous immunogenicity (2) as the factor that is limiting human immunotherapy. With respect to additional means for immune suppression, we almost have too many options from which to choose. A reductive solution to this complexity would be the existence of an immune-suppressive process in the tumor microenvironment that is so stringent that it masks potentially effective antimicrobial immune responses, even in the presence of T-cell checkpoint antagonists. Paradoxically, then, the intermittent, but remarkable, successes of cancer vaccines, T-cell checkpoint antagonists, and adoptive T-cell therapies in patients with solid tumors highlight our ignorance: we do not know the reasons for the failures. Would the answer to this question be revealed by considering elements of the tumor stroma that are shared with the basic "wound healing response"?

Initial Studies of the Role of the Tumoral FAP\(^+\) Stromal Cell

The resemblance of the tumor stroma to chronic inflammation was noted almost 30 years ago by Dvorak in a publication (8) entitled "Tumors: wounds that do not heal." Dvorak raised the possibility that the tissue-protective reactions that have been evolutionarily selected to promote normal tissue regeneration and remodeling occur also in tumors. The inflammation associated with wound healing and tumors has led to many studies of its capacity to promote both the development of cancer (9) and immune suppression by recruiting hematopoietic cells of innate and adaptive immunity. For example, myeloid-derived cells with immune-suppressive function may modify the tumor microenvironment by expressing enzymes, such as nitric oxide synthase 2 and indoleamine 2,3-dioxygenase 1 (IDO1), that interfere with local immune reactions (10–12), whereas M2-polarized macrophages produce immune-suppressive cytokines, such as interleukin (IL)-10 (13). In contrast with the extensive studies of these cell types, the nonhematopoietic stromal cells of "fibroblastic" origin that also accumulate in tumors, which are known as "carcinoma-associated fibroblasts" (CAF; ref. 14), have not been evaluated for immunologic functions. In 1990, Garin-Chesa and colleagues identified an "activated" fibroblast of adenocarcinomas and melanoma by its expression of the "F19" antigen, termed fibroblast activation protein-\(\alpha\), or FAP (15). They also noted that the "expression of the F19 cell surface glycoprotein is a shared characteristic of activated fibroblasts in wound healing, inflammation, and cancer." Further studies of FAP showed that it belongs to the prolyl oligopeptidase subfamily of dipeptidyl peptidases, and is expressed by stromal fibroblasts in a wide range of chronic inflammatory reactions, including rheumatoid arthritis synovial tissue, primary biliary cirrhosis, and atherosclerotic plaques. Thus, for more than 20 years, there has existed a candidate of nonhematopoietic, mesenchymal origin for the role of tumoral immune suppression, the FAP\(^+\) stromal cell.

An early study of the effects on tumor growth of targeting the FAP\(^+\) stromal cell was overly simplistic; it was based on an assumption that DNA vaccination with a plasmid construct expressing FAP would induce immune-dependent elimination of FAP\(^+\) stromal cells by cytolytic CD8\(^+\) T cells (16). The authors reported that reducing tumor-associated fibroblasts by this means improved the sensitivity of transplanted mouse models of colon and breast cancer to chemotherapeutic agents, although neither the generation of FAP-specific CD8\(^+\) T cells nor decreased numbers of FAP\(^+\) cells in tumors were clearly documented. A second report analyzed the function of the membrane protein, FAP, rather than the stromal cell itself (17). These experiments demonstrated that a transplanted colon carcinoma grew more slowly in mice in which the expression of the fap gene was interrupted, and that an inhibitor of dipeptidyl peptidase activity of FAP impaired the growth of an ectopic murine lung tumor. This study, however, did not examine whether the FAP\(^+\) stromal cell had an immune-suppressive function.

The first experiments that assessed the immunologic effects of perturbing the FAP\(^+\) stromal cell used a direct approach of conditionally depleting this cell type from a mouse bearing an immunogenic tumor. A mouse line was generated in which FAP\(^+\) cells were directed to express the diphteria toxin receptor (DTR) by a modified bacterial artificial chromosome.
suppression; and the means by which the FAP is broadly applicable to the question of tumoral immune suppression. However, three aspects of this study highlighted the need for further work: FAP expression is not an identifier only of nonhematopoietic stromal cells; this highly artifactual finding of FAP expression in mesenchymal or hematopoietic origin, or both, accounted for immune suppression in the LL2/OVA model. Using radiation bone marrow chimera mice in which the BAC transgene directing the expression of the DTR was present in either hematopoietic or nonhematopoietic lineages, it was shown that depletion either of CD45+ cells or of CD45+ cells with diphtheria toxin resulted in immune control of LL2/OVA growth (19). The tumoral CD45+ cells have been characterized as a minor subset of the F4/80+/CCR2+/CD206+ macrophages, and they are the major tumoral source of the immune inhibitory enzyme heme oxygenase-1 (HO-1). Immune suppression by the tumoral FAP+ macrophages required the activity of HO-1, and inhibiting it with Sn mesoporphyrin induced a hypoxic form of tumor killing that was mediated by IFN-γ and TNF-α (19). This study indicates that another enzyme expressed by the innate immune cells that accumulate in tumors has immune-suppressive activity. It is of interest that carbon monoxide, one of the products of the catabolism of heme by HO-1, prevents tracheal allograft rejection (20), and that inflammation in a model of immunologically induced arthritis is more severe in mice lacking HO-1 than in wild-type mice (21). Although the latter two studies did not identify the cellular source of HO-1, their findings support the possibility that the HO-1–expressing FAP+ macrophage may have immune-suppressive functions that are beneficial to the host.

An unanticipated level of complexity revealed by this study was the expression of FAP not only by fibroblastic stromal cells, but also by a subset of macrophages. The finding of FAP+ stromal cells with characteristics of macrophages in human breast cancers confirmed their potential clinical importance, and emphasized the necessity of determining whether FAP+ cells of mesenchymal or hematopoietic origin, or both, accounted for immune suppression in the LL2/OVA model. Using radiation bone marrow chimera mice in which the BAC transgene directing the expression of the DTR was present in either hematopoietic or nonhematopoietic lineages, it was shown that depletion either of CD45+ cells or of CD45+ cells with diphtheria toxin resulted in immune control of LL2/OVA growth (19). The tumoral CD45+ cells have been characterized as a minor subset of the F4/80+/CCR2+/CD206+ macrophages, and they are the major tumoral source of the immune inhibitory enzyme heme oxygenase-1 (HO-1). Immune suppression by the tumoral FAP+ macrophages required the activity of HO-1, and inhibiting it with Sn mesoporphyrin induced a hypoxic form of tumor killing that was mediated by IFN-γ and TNF-α (19). This study indicates that another enzyme expressed by the innate immune cells that accumulate in tumors has immune-suppressive activity. It is of interest that carbon monoxide, one of the products of the catabolism of heme by HO-1, prevents tracheal allograft rejection (20), and that inflammation in a model of immunologically induced arthritis is more severe in mice lacking HO-1 than in wild-type mice (21). Although the latter two studies did not identify the cellular source of HO-1, their findings support the possibility that the HO-1–expressing FAP+ macrophage may have immune-suppressive functions that are beneficial to the host.

The general relevance of the LL2/OVA model was demonstrated by studies of the mechanism of immune suppression by the tumoral CD45+ FAP+ mesenchymal cell in an autochthonous model of pancreatic ductal adenocarcinoma (PDA; refs. 22, 23). This genetically engineered "KPC" (LSL-KrasG12D+; LSL-Trp53R172H+; Pdx-1-Cre) mouse model replicates three aspects of the human disease: the molecular features of mutant Kras and loss of heterozygosity at the Trp53 locus; the clinical features of invasiveness and widespread metastases (22); and the resistance to the tumor growth-inhibiting effects of both anti–CTLA-4 and anti–PD-L1 (23). Because the latter characteristic could have been a consequence of the PDA being nonimmunogenic, the study by Feig and colleagues first determined whether the PDA-bearing mice had immunologically responded to the tumor. An enzyme-linked immunosorbent spot (ELISpot) assay revealed that splenic CD8+ T cells from PDA-bearing mice were stimulated to produce IFN-γ by cells from their own tumors and from tumors of other mice, but not by premalignant cells from pancreatic intraepithelial neoplasia (PanIN) lesions expressing KrasG12D and mutant Trp53R172H (23).

Taken together, these findings justify three conclusions about the immune response to this spontaneous murine PDA. First, the adaptive immune response is directed to antigens shared by cancer cells from different tumors, making it likely that they are products of nonmutated genes. Is the expression of "neoantigens" a regulated process rather than an "accident" of the genetic instability of cancers? The finding of a spontaneous anticancer cell immune response in this mouse model is consistent with the favorable clinical response of some patients treated with anti–PD-L1/anti–PD-L1, which strongly suggests preexisting immune responses in these individuals. It is of interest that even though these mice had a demonstrable anticancer cell immune response, they did not respond to treatment with anti–PD-L1 (23). Therefore, one cannot conclude that the absence of a clinical response to this T-cell checkpoint antagonist necessarily indicates an absence of an anticancer cell immune response. Second, the immune response in the PDA-bearing KPC mouse distinguishes between malignant and premalignant PanIN or normal pancreatic epithelial cells, so that overcoming immune suppression might not cause immunologic damage to normal tissues. In this model, both PDA and PanIN express the mutant KrasG12D and Trp53R172H, so that the CD8+ T cells are not specific for these antigens. What is the nature of a nonmutated antigen that is expressed by malignant but not premalignant epithelial cells? Does the hypermetabolic and hyperproliferative state of the cancer cell induce stress that may account for its expression of neoantigens (24)? If so, would this stress response cause the majority of adenocarcinomas to be spontaneously immunogenic, rendering vaccination unnecessary? Third, and most importantly, the continued growth of the PDA in the presence of an ongoing anticancer cell immune response...
and treatment with anti–CTLA-4 or anti–PD-L1 must be interpreted as evidence for the occurrence of an additional immune-suppressive process in the PDA microenvironment that is distinct from these T-cell checkpoints.

The link between this inferred means of immune suppression and the FAP+ stromal cell was demonstrated by the T cell–dependent slowing of PDA growth that occurred when these stromal cells were conditionally depleted (23). The presence in this tumor only of CD45+ FAP+ stromal cells supported the finding in bone marrow chimeric mice bearing LL2/OVA tumors that this fibroblastic type of FAP+ cell is capable of mediating immune suppression (19). Moreover, the expression by the FAP+ cell in the autochthonous PDA of α-smooth muscle actin and the “inflammatory gene signature” of the CAF (25) identified these cells as a stromal cell type that previously had been studied mainly in xenograft models, which

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Response to anti-PD-1/PD-L1</th>
<th>FAP+ cells present</th>
<th>CXCL12 on cancer cells</th>
<th>T cells absent from cancer cell nests</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA (mouse)</td>
<td>0/8 (23)</td>
<td>Yes (23)</td>
<td>Yes (23)</td>
<td>Yes (23)</td>
</tr>
<tr>
<td>PDA</td>
<td>0/14 (4)</td>
<td>Yes (8, 23)</td>
<td>Yes (23, 33)</td>
<td>Yes (8)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0/94 (3, 4)</td>
<td>Yes (8)</td>
<td>Yes (34)</td>
<td>Yes (28)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1/17 (4)</td>
<td>Yes (8)</td>
<td>Yes (35)</td>
<td>Yes (29)</td>
</tr>
</tbody>
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Table 1. Adenocarcinomas that are resistant to a T-cell checkpoint antagonist and exhibit tumoral FAP+ cells, CXCL12, and intraepithelial T-cell exclusion

Figure 1. Accumulation of CD3+ T cells in p53+ cancer cell–containing regions of mouse PDA induced by AMD3100 and anti–PD-L1. Tissue sections from PDA tumors taken from mice that had been treated for 24 hours with PBS, anti–PD-L1, AMD3100, or AMD3100 + anti–PD-L1 were stained for CD3 and p53 and analyzed by immunofluorescent microscopy. The PDA cancer cells are p53+ because they have lost the wild-type p53 allele, which stabilizes the p53R172H protein (figure modified from ref. 23: Feig et al. Proc Natl Acad Sci U S A 2013;110:20212–7).
Immune Suppression by Exclusion of T Cells: The Tissue-Protective Role of CXCL12

The function of T cells that is affected by the FAP+ CAF was discovered to be their ability to accumulate among cancer cells, which was markedly impaired in murine PDA (Fig. 1). The phenomenon of T-cell exclusion from "cancer cell nests" would account for the inability of a systemic immune response to control tumor growth, and for the absence of a response to anti-PD-L1 in the murine PDA model. In addition, this stringent means for escape from immune surveillance has been noted in other cancers, including the murine B16 melanoma model (27) and human colorectal (28), ovarian (29), and lung cancers (ref. 30; Table 1), raising the possibility of a shared mechanism for the resistance of these three human cancers to anti-PD-1/anti-PD-L1 (3, 4). The mechanism of exclusion in the murine PDA model has been shown to involve CXCL12. This chemokine is biosynthesized in the tumor mainly by the FAP+ CAF (23, 26), but becomes physically associated with the PDA cancer cells. Although the means of association has not been proven, it may be mediated by the DNA-binding high mobility group box 1 protein (HMGB1), with which CXCL12 is known to form a heterodimer (31). HMGB1 has been shown to be overexpressed and secreted by metabolically stressed cancer cells, but this response has been considered to be proinflammatory rather than tissue-protective (32). Because T cells express CXCR4, the receptor for CXCL12, and were absent from the tumoral regions containing CXCL2 protein, it was logical to study the effects on T-cell exclusion in the murine PDA of AMD3100/plerixafor, a CXCR4 inhibitor that was developed for blocking the binding of X4-tropic strains of HIV and is now clinically approved for the recovery of hematopoietic stem cells. Within 24 hours, the administration of AMD3100 induced a redistribution of CD3+ T cells, which included those that were CD4+, CD8+, and Foxp3+, into the regions in the tumor that contained cancer cells (Fig. 1). This redistribution caused by AMD3100 had two functional consequences: the arrest of PDA growth, and an uncovering of the efficacy of a T-cell checkpoint antagonist as shown by a synergistic reduction in tumor volume when anti-PD-L1 was coadministered. After 6 days of combined therapy with AMD3100 and anti–PD-L1, essentially all cancer cells had been eliminated from the PDA tumors, leaving a residual tumor mass comprising premalignant PanIN, inflammatory cells, and the typical desmoplasia of PDA (23).

These preclinical studies may inform the debate concerning how best to intervene immunologically in certain human cancers. In addition to the current emphases on T-cell checkpoint antagonists, vaccination, and adoptive T-cell therapy, oncologists may now begin to consider therapies that overcome T-cell exclusion from cancer cell nests as a means of immune escape. The literature has described this phenomenon in colorectal cancer in 1998 (28), in ovarian cancer in 2003 (29), and now in PDA (23). The next step is to determine whether these studies in the mouse model of PDA are relevant to these three human adenocarcinomas in which not only T-cell exclusion has been documented, but also the association of CXCL12 with cancer cells (Table 1). This mechanistic approach to overcoming the block to intratumoral accumulation of cancer-specific CD8+ T cells has the potential not only to enable a spontaneous anticancer cell immune response to control tumor growth, but also to enhance, when necessary, any T-cell–directed immunologic intervention, including checkpoint antagonists, adoptive T-cell therapy, inhibitors of IDO, and vaccination.

These studies indicate that the FAP+ CAF presents a block to T cells not by its creation of a physical barrier comprising the collagen-rich, desmoplastic reaction but by its biosynthesis of CXCL12 that coats cancer cells to form a biochemical barrier. We need to understand how the ligation of CXCR4, presumably on T cells, by CXCL12 on the cancer cells restricts the accumulation of T cells in the stromal regions of the tumor. Existing literature presents two possible ways that this might occur: apoptosis of T cells, as was reported for HIV gp120 interacting with CXCR4 (36), and T-cell chemorepulsion (37). Undoubtedly, this CXCL12/CXCR4–dependent means for blocking immune attack evolved for the protection of normal tissues, and defining precisely how it suppresses the local accumulation of T cells may lead to improved treatments for autoimmune and infectious diseases. Inhibiting CXCR4 with AMD3100 has already been demonstrated to enhance immune control of mouse West Nile virus encephalitis (38). It would be of interest to determine whether the antigens expressed by the PDA cells reflect a physiologic response to the stress-induced unfolded protein response in the endoplasmic reticulum that may occur during tissue injury and regeneration (24).

Studies of the FAP+ Stromal Cell in Normal Tissues

The first identification of FAP-expressing cells noted their presence in adenocarcinomas and surgical incision wounds, but not in a range of normal tissues and epithelial organs (8). A subsequent study of mouse embryos in which the lacZ reporter was inserted into the fap gene showed β-galactosidase expression in somites and perichondrial mesenchyme from cartilage primordia, but did not comment on the expression of the lacZ marker in adult knockin mice (39). Another study assessing colorectal patients receiving 131I-labeled anti-FAP antibody reported no uptake by normal tissues, which was interpreted as indicating that the FAP protein was absent from normal tissues (40). Therefore, it was surprising when the bioluminescent signal of BAC transgenic mice in which the fap gene controlled expression of luciferase was demonstrated in almost all tissues of the...
adult mouse (41). This finding of a wide tissue distribution of FAP\(^+\) stromal cells was confirmed by mRNA measurements and by fluorescence-activated cell sorting (FACS) analyses of single-cell suspensions of selected tissues and organs stained with anti-FAP antibody. The FAP\(^+\) stromal cells from adipose tissue, skeletal muscle, and pancreas had transcriptomes that were highly similar, suggesting a common mesenchymal lineage, and were even similar to the transcriptomes of FAP\(^+\) stromal cells from the regions of the mouse KPC tumor that contained premalignant and malignant pancreatic ductal cells. These FAP\(^+\) stromal cells from normal tissues, especially those from adipose tissues, also exhibited the "inflammatory" gene signature of the CAF (25), suggesting that they may have roles in promoting innate immune responses in normal tissues as well as in neoplastic lesions, perhaps for the purpose of tissue regeneration following injury.

In addition to their potential activities in regulating inflammation, FAP\(^+\) stromal cells have essential homeostatic functions (41). FAP\(^+\) cells of skeletal muscle are the major local source of follistatin, which is required to maintain muscle mass by inhibiting myostatin and activin A signaling in this tissue. In the bone marrow, FAP\(^+\) cells express CXCL12, IL-7, and KitL, identifying them as "CXCL12-associated reticular" cells (42). Experimental ablation of FAP\(^+\) cells from the skeletal muscle and bone marrow causes loss of muscle mass and a reduction of B-lymphopoiesis and erythropoiesis, respectively. The fibroblastic reticular cell of the T-cell zone of lymph nodes and Peyer’s patches, but not the spleen, also is FAP\(^+\), and their conditional depletion causes the loss of lymph node but not splenic T and B cells (A.E. Denton and D.T. Fearon; submitted for publication). Osteoblasts also are FAP\(^+\), whereas FAP-expressing cells in the stromal vascular fraction of adipose tissue can be identified as precursor adipocytes based on their expression of Fapb4. The latter observation suggests that adipocytes, which do not express FAP, may be derived from FAP\(^+\) precursors.

This demonstration of FAP\(^+\) cells in normal tissues may advance the understanding of complex pathologic responses. For example, FAP\(^+\) cells are altered in skeletal muscle and the bone marrow in transplanted and spontaneous mouse models of cancer-induced cachexia and anemia, suggesting that they may have roles in these poorly understood cancer-induced syndromes (41). Fortunately, the discovery of the FAP\(^+\) lineage and its essential homeostatic functions occurred before the consideration of depleting FAP\(^+\) cells, as a means for overcoming tumoral immune suppression had advanced to a human clinical program. The experiments in which DTR-expressing FAP\(^+\) stromal cells were conditionally depleted predicted a potentially disastrous outcome, an expectation that has been confirmed by one study in a mouse model finding anemia and skeletal muscle loss caused by adoptively transferred T cells with CARs specific for FAP (43), although not by another study (44) for reasons that are not clear. In any event, the demonstration that one can target a single product of the FAP\(^+\) CAF, CXCL12, rather than the cell itself to overcome immune inhibition renders unnecessary this less-specific approach. The scientific payoff of identifying the dominant immune-suppressive function of the FAP\(^+\) CAF was that one could then focus on this cell alone among the many present in the tumor stroma to discover how cancer cells escape immune control.

**Future Studies**

The critical next step is to assess the clinical effects of blocking the interaction of CXCL12 with CXCR4 in patients with PDA and possibly other cancers in which FAP\(^+\) CAFs are present and cancer cells are coated with CXCL12. A clinically approved drug, AMD3100 (plerixafor), is available for this purpose. Clearly, we must understand the mechanism by which ligation of CXCR4 excludes T cells from regions of the tumor microenvironment that contain cancer cells. We must also uncover the means by which cancer cells bind CXCL12, as this may provide insight into how epithelial cells may protect (or not) themselves from immune attack in autoimmune diseases. Finally, the definition of the antigens in murine PDA that elicit the immune response may uncover basic molecular pathways by which cells induce autoimmune responses. The continued interaction between the oncology and immunology communities promises to be exciting.

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Douglas T. Fearon


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