Chemokines in the Landscape of Cancer Immunotherapy

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“Hot” tumors are those that show signs of inflammation, meaning they have been invaded by effector T cells rushing to fight the cancerous cells. Evidence suggests that the limited success of ICI-based immunotherapies is related to attempts to treat patients with “cold tumors” that either do not contain effector T cells or in which these cells are markedly suppressed by regulatory T cells (Tregs). Chemokines are a well-defined group of proteins with chemotactic properties. We focus on key chemokines that not only attract leukocytes to tumor sites but also shape their biological properties. We propose using stabilized forms of two of them: CXL9 and CXCL10, to enhance anti-tumor immunity and possibly transform cold tumors into hot ones. Additionally, we discuss the possibility of targeting or deleting a key subset of Tregs that are CCR8+ Tregs and are highly dominant at the tumor site of several cold tumors. This may convert these cold tumors into hot tumors, and thus extend the success of immunotherapy beyond its current limits.

chemokines chemokine receptors cancer immunotherapy CXCL9 CXCL10 CCR8 CCL1 regulatory T cells immune checkpoint inhibitors

1. Introduction

Chemokines are small proteins that have mostly been associated with directing leukocyte migration, and in affecting the dynamics of cancer, inflammation, and immune regulation [1][2][3]. As for cancer, many chemokines are produced by cancer cells that also possess their receptors [4][5]. So far, sixteen out of nineteen human chemokine receptors have been detected in cancer cells [6]. Key examples are CXCR4, CXCR1/2, CCR2, CXCR3, CCR5, and their ligands [1]. All became targets for cancer therapy [1][4][5][7][8][9]. The traditional view has been that chemokines mostly support tumor growth and survival either by a direct effect on tumor cells that possess their receptors [5] or by indirect mechanisms [5][10][11][12][13][14]. These indirect mechanisms mostly include interactions with their receptors on endothelial cells within the tumor microenvironment (TME), to induce growth factors production, and also in attracting bone marrow (BM)-derived cells to the tumor site. These cells then assist tumor growth and suppress the activities of anti-tumor effector T cells that limit tumor growth [5][10][11][12][13][14]. The major BM-derived cells that are known to support tumor growth and suppress anti-tumor immune reactivity are tumor-associated macrophages (TAMS), myeloid-derived suppressor cells (MDSC), neutrophilic cells, and regulatory T cells (T_{regs}). All of them suppress anti-tumor immune reactivity, and some of them directly support tumor growth [5][10][11][12][13][14]. Altogether, it implies that chemokines and their receptors are valid targets for cancer therapy [15]. Yet, thus far attempts to block many of these chemokines or their receptors showed limited success in human cancers. A

possible mechanism of tumor escape may involve the rapid selection of resistant tumor cells [4]. The other possible explanation could be redundancy between chemokines [16][17].

The breakthrough of using monoclonal antibodies to immune checkpoint inhibitors (ICI) (also referred to as immune checkpoint blockers, ICB) opened new therapeutic opportunities [18][19][20][21][22][23][24][25][26]. The first successful approach of ICI has been the use of anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors in metastatic melanoma [25][27][28][29][30], and continuing with blocking the interactions between program cell death 1 (PD-1) and its ligands: program cell death ligand 1 (PDL-1) and program cell death ligand 2 (PDL-2) [25][27][28][29][30]. These blockers have been approved for about 20 different indications [23][26][31][32][33][34][35][36]. As a part of their mechanism of action, these ICIs enhanced the activity of tumor-specific effector $CD4^+$ and $CD8^+$ T cells [31][32][34][37]. Yet, immune checkpoint therapies (ICT) for many cancer diseases still show limited success [21][31][38][39][40][41]. Moreover, even in diseases with a significant positive response to ICI a relatively high number of patients are poor responders, and/or develop severe immune-related toxicities. This led to intensive research in two complementary avenues. The first focuses on developing tools for personalized-based medicine enabling to predict success on a personalized basis and excludes patients that following therapy have a high risk of developing immune-related toxicities [42][43][44][45][46][47][48]. The other avenue is spending efforts on developing new immunotherapeutic tools that would be used, either alone, or in combination with “conventional” ICI, and extend their therapeutic landscape.

It is believed that one of the major reasons for which the success of ICI is limited is that therapy is applied on diseases that either lack infiltration of effector $CD8^+$ T cells or include massive accumulation of T_{regs} that suppress their activities [26][31][32][33][34][35][36]. These tumors are known as “cold” tumors [49][50][51]. Turning “cold tumors” into “hot tumors” by enhancing the activity of tumor-specific infiltrating effector T cells may extend the relative number of responders to ICI [49][50][51][52]. Likewise, in tumors enriched with T_{regs}, it is likely that blocking their activity or depleting these cells from the TME would turn cold tumors into hot.

2. Regulatory T Cells in Cancer Diseases, and Chemokine Receptor-Based Selective Depletion of These Cells for Cancer Immunotherapy

Maintenance of immunological self-tolerance by suppressing self-reacting T cells, as well as restraining the activities of effector T cells in response to infectious stimuli, thus, limiting chronic inflammatory conditions, is largely regulated by $CD4^+$ regulatory T cells; [53][54]. These cells fall into two major subsets: those that express the transcription factor forkhead box P3 (FOXp3), also known as regulatory T cells (T_{regs}), and those that are FOXp3-negative but produce high levels of IL-10, also known as T regulatory -1 cells (Tr1) [53][54][55]. Those that are FOXp3+ commonly do not express the IL-7 alpha chain CD127, which is essential for IL-7 signaling required for converting T cells into memory cells [56][57][58]. These cells are of major interest for their key role in regulating cancer disease, mostly in suppressing the anti-cancer reactivity of effector T cells [59]. There are three major approaches for inhibiting T_{regs} and their ability to limit anticancer effector T cells: 1. Blocking the migration and accumulation of T_{regs} at the tumor site. 2. Inhibiting their suppressive activities within the tumor site and 3. Depletion of T_{regs} within the tumor site. Of these approaches, depleting T_{regs} is likely to be the most dramatic and

possibly effective way. Yet systemic depletion of T_{regs} may result in major impairment of immune regulation. For example, a loss-of-function mutation in the gene encoding FOXp3 leads to a very severe autoimmune syndrome in humans named immune deficiency poly-endocrinopathy enteropathy X-linked (IPEX) syndrome [60].

Chemokines and chemokine receptors are thought to be involved in the selective migration of T_{regs} to the tumor site, and also in their potentiation within this site. T_{regs} express several chemokine receptors among them: CCR8, CCR4, CXCR3, CCR2, CCR6, and CCR5 [61]. Among these receptors, the CCR4-CCL22/CCL17 and the CCR8-CCL1 axis have been of major interest for both selective migrations of T_{regs} to tumor sites and their potentiation there. Moreover, their selective accumulation within the tumor site may suggest that selective depletion of $CCR4^+$ or $CCR8^+$ T_{regs} may enhance anti-cancer immunity while having a very limited effect on T_{regs} in the periphery. This subject is further discussed below.

2.1. $CCR4^+$ T_{regs}

CCR4 is a chemokine receptor with two ligands CCL22 and CCL17. Both ligands but mostly CCL22 are largely involved in directing the recruitment and induction of suppressive function of T_{regs} at the tumor site [62][63][64][65][66][67][68][69][70][71]. This includes breast cancer, cervical cancer, glioblastoma, squamous cell carcinoma (SCC) colorectal cancer (CRC), and Pancreatic ductal adenocarcinoma (PDAC) [62][63][64][65][66][67][68][69][70][71]. Aside from T_{regs}, CCR4 is present in other leukocytes, among them $CD4^+$ Th2 cells, NK cells, and macrophages [70][72][73][74]. It is also abundant on cancer cells, among them breast cancer [67]. Olkhanud et al. used a highly metastatic breast cancer (4T1) model in which CCR4 is largely expressed on cancer cells and T_{regs}, and demonstrated the pivotal role of CCR4 in recruiting and inducing NK cells and T_{regs} to limit tumor development and metastatic spread [71]. This does not exclude the possibility that targeting CCR4 would be more effective in several cancer diseases in which cancer cells are also $CCR4^+$, among them breast cancer. In human cancers, major target diseases are several solid tumors, B-cell lymphomas, T-cells lymphomas, and leukemia in which not only CCR4 is highly expressed within the tumor microenvironment by T_{regs}, NK cells, and tumor cells, but mostly in those that poor prognosis has been associated with high expression of CCR4 on these cells [66][67][75][76][77][78]. Currently, there are two small chemical class II antagonists produced by Astra-Zeneca that block T_{regs} recruitment (AZD-2098, Marketed, and AZD-1678 in preclinical studies), a small chemical class II antagonist that blocks the interaction between CCL22 and CCR4 (FLX-475 produced by FLx-Bio) in phase 1/2 clinical trials as monotherapy or in combination with anti-PD-1 (Merck), a humanized mAb (KW-0761) capable of inducing ADCC to $CCR4^+$ cells in phase 1a monotherapy for solid tumors, in combination with anti-PD-1 (Merck) for B cell lymphoma (phase 1/2), in combination with anti-PD-L1 or anti-CTLA-4 (Astra-Zeneca) in Phase 1b for solid tumors, and combination with anti-PD-1 (BMS) for solid tumors (very recently reviewed in [61]).

2.2. $CCR8^+$ T_{regs}

CCR8 is a chemokine receptor mostly, but not exclusively, expressed by FOXp3+ T_{regs} [72][79][80][81][82][83]. Human CCR8 has four known ligands: CCL1, CCL8, CCL16, and CCL18 [84], whereas in murine only 3 of them are expressed: CCL1, CCL8, and CCL16 [85][86][87]. In both humans and mice, CCR8 is the only known receptor for

CCL1 [80], whereas the other CCR8 ligands bind several chemokine receptors, as well as decoy receptors [85][86][87]. Four years ago, we identified CCR8$^+$ T_{regs} as master drivers of the immune regulation [88]. In this study, we observed that the relative number of CCR8$^+$ T_{regs} that is very low in the periphery increases along with the development of experimental autoimmune encephalomyelitis (EAE), a T cell-mediated autoimmune disease of the central nervous system (CNS). This study also observed that within the CNS CCR8$^+$ T_{regs} are potentiated by CCL1, possibly in an autocrine manner, which makes them “driver” regulatory cells that restrain the progression of the disease [88]. Independently, Plitas et al. showed that in several human tumors, particularly “cold tumors” such as breast cancer, that these cells are highly dominant [89]. Along with this, recently it has been reported that anti-CCR8 mAb could be used to limit cancer growth in several cancer models [90][91][92]. One of the major reasons for which the success of ICI is limited is that therapy is applied on diseases that are designated as “cold tumors” that either lack infiltration of effector CD8$^+$ T cells, or include massive accumulation of T_{regs} that suppress their activities [49][50][93][94][95][96]. Anti CCR8 mAb, mostly depleting antibodies, are currently under preclinical development by several lead companies.

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