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Short Communication

FGF2- Mediated Programming of Macrophages: A Novel Target for Cancer Therapy

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ABSTRACT

Macrophages are present in essentially all cancers. In general these Tumor Associated Macrophages (TAMs) facilitate the growth of cancers, suppress the anti-cancer immune response and promote angiogenesis. Because of these tumor promoting actions, targeting macrophages is a promising, but mainly unrealized strategy for cancer therapy.

Keywords: Macrophages; Cancer therapy; Angiogenesis

DESCRIPTION

In Im *et al.* we found that TAMs are responsive to FGF2 [1-3]. Blocking FGF2 prevented immunosuppression in several murine tumor models and greatly enhanced the efficacy of radiation therapy. At the same time FGF2 blockade altered the polarization of TAMs reducing their pro-tumor effects. FGF2 has long been known as a potent angiogenic factor, although in cancer it is often not the driver of angiogenesis. Despite its presence in cancer, increased FGF2 is not always associated with increased vascularity [4–6]. FGF2 had not previously been identified as a modulator of macrophages polarization nor been shown to influence anti-cancer immunity.

Macrophages, which are present in almost every tissue can differentiate or be polarized along a spectrum with pro-inflammatory characteristics sometimes called M1 or a wound healing state or immunosuppressive state- M2 [1]. Tumor-Associated Macrophages (TAMs) are the most abundant immune cells in a range of solid tumors [2]. Experimental evidence suggests that TAMs are often skewed towards an M2-like pro-tumorigenic phenotype but still can harbor inflammatory characteristics. Phenotype, survival, and proliferation of TAMs depends upon tumor microenvironmental stimuli including tumor derived cytokines such as Macrophage Colony-Stimulating Factor (M-CSF), Granulocyte-Macrophage CSF (GM-CSF) and Transforming Growth Factor Beta 1(TGF-β1) [7–9]. It is thus plausible that alterations of tumor microenvironmental signals could profoundly result in the programming of TAMs and thereby affect tumor growth and response to therapy.

Multiple methods have been evaluated to induce M1 polarization in TAMs. Targets have included receptors and intracellular signaling such as Toll-Like Receptors (TLRs), CD40 and M-CSFR [9-13]. Stimulation of TLRs activates NF-κβ, STAT1, AP-1 and IRF3 and leads to activation of M1-associated genes. Imiquimod (TLR7 agonist) is under phase 2 and 3 clinical trials for breast cancer and cervical intraepithelial cancer respectively [9]. CD40 expressed on the surface of myeloid cells and B cells plays a key role in immune regulation [14]. In clinical trials CD40 mAb combined with chemotherapy resulted in increased overall survival of patients having pancreatic ductal adenocarcinoma [9]. M-CSFR inhibitors have been used for macrophage depletion and tumor regression in pre-clinical models. In some clinical trials blocking M-CSFR with antibodies resulted in stabilization of glioblastoma and breast cancer, but other studies reported only reduction of TAMs without any improvement in tumor control [15–17].

Intracellular signaling of TAMs can be altered via modifications of nucleic acids, cellular kinase or Histone Deacetylase (HDAC) with small molecules or antisense MicroRNA (miRNA) [9]. Vorinostat is a broad HDAC inhibitor which suppresses class I and II HDAC enzymes, but not class III enzymes. It was approved by FDA for use in treatment of T-cell lymphoma [1,9,18,19]. Several COX2 inhibitors including NS-398, Etodolac and Celecoxib disrupted Prostaglandin 2 (PGE2) signaling and induced an inflammatory M1-like phenotype in macrophages [1,20-22]. Inhibition of Bruton's Tyrosine Kinase (BTK) or PI3Kγ signaling with

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ibrutinib and TG100-115 respectively, skewed TAMs towards an M1- pro-inflammatory phenotype which increased expression of IL-12 and decreased TGF-β and ARG1 in vitro. Ibrutinib is used clinically to treat mantle cell lymphoma and chronic lymphocyte leukemia [23]. Recently, miRNAs, small noncoding RNA fragments such as miRNA-155 and miRNA-125b are emerging as important regulators of macrophage polarization. Tumor cells transfected with miRNA shifted recruited macrophages from M2 to M1 [1,24,25]. In addition, Seif *et al.* showed that delivery of TNF-α RNA and MyD88 with recombinant *Saccharomyces cerevisiae* to M2 macrophages resulted in reprogramming of M2 macrophages to an antitumor M1 phenotype [26].

DISCUSSION

Our work with FGF2 showed that it could also provide a target for altering TAMs to a less pro-tumor state. Our work showed that FGF2 expression affected the polarization and function of macrophages within the tumor. Tumors formed in mice genetically deficient in low-molecular-weight FGF2 ($Fgf2^{LMW-/-}$) regressed due to generation of anti-tumor immunity and tumors were substantially more responsive to radiation therapy when a blocking antibody to FGF2 was administered. TAMs were the primary source of FGF2 in tumors (about 83%), while MDSCs or granulocytes expressed less of the total FGF2, 9.7% and 29.9% respectively [3]. TAMs also expressed receptors for FGF2 with approximately 85% expressing FGFR1 and FGFR2 while naïve macrophages did not. The TAMs from $Fgf2^{LMW-/-}$ mice had a significant increase in the M1 or inflammatory phenotype compared to TAMs from wild type mice. And the combination of radiotherapy and anti-FGF2 antibody consistently led to increased repolarization of TAMs with an increased (M1/M2) macrophage ratio along with greater tumor response than with radiotherapy alone. In this study FGF2 altered macrophage programming and as a consequence of its action on macrophages was an important regulator of immunity in the tumor microenvironment.

CONCLUSION

Reprograming from the M2- to the M1-like phenotype coincided with reduced tumor growth and immune-mediated tumor regression. This work suggests that FGF2 in the tumor microenvironment is an important regulator of macrophage differentiation, and may play a particularly important role during radiation therapy. FGF and FGFR present themselves as novel targets for macrophage programming in tumors.

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