Introduction

The macrophages that infiltrate neoplastic lesions play a key role in the survival, proliferation, and progression of malignant cells. Unlike traditional macrophages, tumor-associated macrophages (TAMs) have been reprogrammed by the tumor microenvironment to mediate limited cytotoxic and antigen-presenting functions, hence allowing for tumor growth and progression. One elegant study has demonstrated that interleukin-1β (IL-1β) mediates a cross-talk between TAMs and prostate cancer cells that promotes the resistance of the latter to hormonotherapy as it alters the sensitivity of the androgen receptor (AR) to specific inhibitors. Thus, TAMs also modulate the biological activity of the AR in prostate cancer cells. Conversely, androgen withdrawal in patients with prostate cancer promotes tumor infiltration by various immune cell subsets, including T cells and macrophages, which may underlie the inflammatory responses developing within prostate malignancies upon such a therapeutic intervention. However, little is known on how the AR, a major driver of prostatic oncogenesis and tumor progression, crosstalk with inflammatory signals in this setting. Interestingly, androgen ablation has been shown to elicit the recruitment of various leukocyte subsets into prostate neoplasms, eventually resulting in the development of castration resistance upon the secretion of lymphotoxin by B cells. Macrophages were also identified within prostate cancers in this study, but it was not clear whether TAMs or their cytokines were involved in the development of castration resistance. These findings indicate that castration may promote the recruitment of macrophages to the prostate tumor microenvironment, perhaps resulting in the emission of inflammatory signals that could be important for the development of resistance. However, it remains to be determined if the AR is specifically involved in this process, since androgen deprivation therapy (ADT) may have a global impact on a variety of cells of the tumor microenvironment. We believe that understanding the molecular mechanisms whereby the inhibition of AR signaling regulates the inflammatory tumor infiltrate may assist the design of novel strategies to maximize the clinical benefits obtained by prostate cancer from ADT.

AR Downregulation Promotes the Secretion of CCL2 and the Accumulation of M2 Macrophages

Recently, we have determined if the inhibition of the AR in the tumor microenvironment would result in the activation of specific inflammatory signaling pathways that could support the growth and progression of prostate cancer. By means of western blot-based cytokine arrays, we identified chemokine (C-C motif) ligand 2 (CCL2) as a downstream target of silencing the AR by small-interfering RNAs in prostate cancer cells or macrophages. Robust CCL2 expression positively correlates with tumor infiltration by various immune cell subsets, including TAMs and prostate cancer cells or tumor-infiltrating macrophages.

Keywords: androgen receptor; CCL2; epithelial-to-mesenchymal transition; prostate cancer; STAT3

High levels of chemokine (C-C motif) ligand 2 (CCL2) promote the metastatic dissemination of prostate cancer by recruiting macrophages to neoplastic lesions. We have recently discovered that inhibiting the androgen receptor (AR) in prostate cancer cells or tumor-infiltrating macrophages results in the upregulation of CCL2 and promotes disease progression by activating signal transducer and activator of transcription 3 (STAT3) and by favoring the epithelial-to-mesenchymal transition. Our results indicate that the sole inhibition of AR as a therapeutic intervention against prostate cancer is intrinsically destined to failed.

*Correspondence to: Wen-Jye Lin; Email: hydroxyflutamide@gmail.com
Submitted: 01/09/2014; Accepted: 01/15/2014; Published Online: 02/14/2014
Citation: Lin W, Izumi K. Androgen receptor, ccl2, and epithelial-mesenchymal transition: a dangerous affair in the tumor microenvironment. OncoImmunology 2014; 3:e27871; http://dx.doi.org/10.4161/onci.27871
**Figure 1. Disease-promoting effects of androgen receptor inhibition in prostate cancer.** Targeting the androgen receptor (AR) in prostate cancer cells promotes the expression of chemokine (C-C motif) ligand 2 (CCL2), the recruitment of macrophages, the activation of signal transducer and activator of transcription 3 (STAT3), hence the epithelial-to-mesenchymal transition. Altogether, these alterations promote disease progression.

Most importantly, we found that silence the AR in prostate cancer cells promotes the phosphorylation-dependent activation of STAT3, hence driving the EMT. It had previously been shown that STAT3 can stimulate the secretion of CCL2 by cancer cells and support the acquisition of stem cell-like features that may resistance to ADT.\(^8,9\) It remains to be determined if the activation of STAT3 by CCL2 truly promotes stem cell-like features among prostate cancer cells, hence favoring metastatic dissemination and hormonal resistance. Our results suggest that CCL2 and STAT3 may engage in a positive feedback loop in AR-depleted prostate cancer cells. The major finding of our study is that the CCL2-STAT3-EMT axis may serve as a means for prostate cancer cells to escape androgen deprivation. We postulate that STAT3 could constitute a point of convergence between signaling pathways that are crucial for the development of the castration resistance and metastasis. In summary, our study indicates that ADT might have both local and global effects that promote prostate cancer progression. Our findings increase our understanding of the molecular mechanisms linking CCL2, tumor infiltration by macrophages and the pathogenesis of castration-resistance prostate cancer (Fig. 1). The underlying signal transduction cascade represents a candidate target for the development of new therapeutic agents to be tested in combination with ADT against prostate cancer.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

This work was supported by US DOD Grant (W81XWH-10-1-0300).

**References**

1. Balkwill F, Charles KA, Mantovani A. Smoldering inflammation in the initiation and promotion of malignant disease. Cancer Cell 2005; 7:211-7; PMID:15766659; http://dx.doi.org/10.1016/j.ccr.2005.02.013

2. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006; 124:263-6; PMID:16439202; http://dx.doi.org/10.1016/j.cell.2006.01.007

3. Zhu P, Baek SH, Bourk EM, Ogbi KA, Garcia-Bassets I, Sanjo H, Akira S, Kotol PF, Glass CK, Rosenfeld MG, et al. Macrophage/cancer cell interactions mediate hormone resistance by a nuclear receptor derepression pathway. Cell 2006; 124:615-29; PMID:16469706; http://dx.doi.org/10.1016/j.cell.2005.12.032
4. Mercader M, Bodner BK, Moser MT, Kwon PS, Park ES, Manecke RG, Ellis TM, Wojcik EM, Yang D, Flanigan RC, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. Proc Natl Acad Sci U S A 2001; 98:14565-70; PMID:11734652; http://dx.doi.org/10.1073/pnas.251140998

5. Ammirante M, Luo JL, Grivennikov S, Nedospasov S, Karin M. B-cell-derived lymphotixin promotes castration-resistant prostate cancer. Nature 2010; 464:302-5; PMID:20220849; http://dx.doi.org/10.1038/nature08782

6. Loberg RD, Ying C, Craig M, Yan L, Snyder LA, Pienta KJ. CCL2 as an important mediator of prostate cancer growth in vivo through the regulation of macrophage infiltration. Neoplasia 2007; 9:556-62; PMID:17710158; http://dx.doi.org/10.1593/neo.07307

7. Roca H, Varsos ZS, Sud S, Craig MJ, Ying C, Pienta KJ. CCL2 and interleukin-6 promote survival of human CD11b+ peripheral blood mononuclear cells and induce M2-type macrophage polarization. J Biol Chem 2009; 284:34342-54; PMID:19833726; http://dx.doi.org/10.1074/jbc.M109.042671

8. Tsuyada A, Chow A, Wu J, Somlo G, Chu P, Loera S, Luu T, Li AX, Wu X, Ye W, et al. CCL2 mediates cross-talk between cancer cells and stromal fibroblasts that regulates breast cancer stem cells. Cancer Res 2012; 72:2768-79; PMID:22472119; http://dx.doi.org/10.1158/0008-5472.CAN-11-3567

9. Sun Y, Wang BE, Leong KG, Yue P, Li L, Jhanjhuwala S, Chen D, Seo K, Modrusan Z, Gao WQ, et al. Androgen deprivation causes epithelial-to-mesenchymal transition in the prostate: implications for androgen-deprivation therapy. Cancer Res 2012; 72:527-36; PMID:22108827; http://dx.doi.org/10.1158/0008-5472.CAN-11-3004