Linking inflammation and neuroendocrine differentiation: the role of macrophage migration inhibitory factor-mediated signaling in prostate cancer

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Abstract
A new paper by Tawadros et al. in Endocrine-Related Cancer demonstrates a link between macrophage migration inhibitory factor and neuroendocrine differentiation in prostate cancer. This paper may have implications in explaining the effect of prostatitis and chronic inflammation on the development of aggressive prostate cancer.

Prostatitis, or inflammation of the prostate, may occur in men as young as 40, or even younger, while prostate cancer and benign prostatic hyperplasia (BPH, or enlargement of the prostate) are most often diagnosed in men above 50. While prostatitis has never been formally established as a cause of prostate cancer, very often men who suffer from prostatitis tend to develop prostate cancer later on in life. Studies have demonstrated an increased risk of prostate cancer in men with symptomatic prostatitis (Dennis et al. 2002, Roberts et al. 2004). This includes risk from bacterial and other infections (Cheng et al. 2010). However, due to a lack of causative factors, the links have never been formally established, despite studies showing that inflammation is frequently present in prostate biopsies, radical prostatectomy specimens, and tissue resected for treatment of BPH (Platz & De Marzo 2004). Common anti-inflammatory drugs were found to lower the levels of serum prostate-specific antigen (PSA), a marker of prostate cancer progression (Chang et al. 2010).

Although no relation between the use of antibiotics, aspirin, or NSAIDs and the risk of prostate cancer could be determined (Daniels et al. 2009), a Phase II trial of the potent anti-inflammatory drug celecoxib (a COX-2 inhibitor) suppressed PSA progression in patients who experienced biochemical progression following radical prostatectomy or radiation therapy (Pruthi et al. 2006). These studies further indicate a relationship between inflammation and prostate cancer.

Despite epidemiological evidence, until now, the mechanism linking these two events has been lacking.
In recent times, various inflammatory cytokines have been found to mediate the proliferation of prostate cancer cells, such as IL6 (Dutt & Gao 2009) and the macrophage inhibitory cytokine (MIC1; GDF15) gene (Dubey et al. 2012). Another important regulator of prostate cancer progression now appears to be the macrophage migration inhibitory factor (MIF), also known as glycosylation-inhibiting factor, a pro-inflammatory cytokine and an important regulator of innate immunity (Nishihira et al. 2003). MIF is released into circulation following infection, glucocorticoid release, or trauma. This cytokine has been implicated in the development and progression of multiple types of tumors. Significantly, this cytokine appears to have a biphasic response: MIF produced by stromal cells but not by tumor cells regulates angiogenesis in various cancers (Verjans et al. 2009, Girard et al. 2012).

The role of MIF in prostate cancer development and progression is not unknown. As early as 1996, investigators have shown that this gene may regulate prostate cancer metastasis (Meyer-Siegler & Hudson 1996). Another early study has shown neuroendocrine differentiation (NED) and MIF expression by the COX-2 inhibitor NS-398 (Meyer-Siegler 2001). The effect of MIF in the cell is mediated by its receptor CD74 (Meyer-Siegler et al. 2006); however, the mechanism by which this cytokine plays a role in prostate cancer progression had not been elucidated.

This missing link has now been provided by Tawadros et al. (2013) in the February issue of Endocrine-Related Cancer. This group has for long been interested in the study of NED in prostate cancer (Tawadros et al. 2005) and has now shown that MIF activates proliferation and survival through the stimulation of Akt and ERK pathways. Neuroendocrine (NE) cells are a component of the normal prostate, and many of the factors shown to be produced by NE cells are known to support growth and differentiation in the prostate (Nelson et al. 2007). Both benign prostate and malignant prostate depend upon the androgen receptor (AR) for growth and survival; hence, androgen deprivation therapy is a cornerstone of treatment for advanced, especially metastatic, prostate cancer (Ruizeveld de Winter et al. 1994, Culig et al. 2000). The expression of the AR in NE tumors is slightly different. Benign and malignant prostatic tissues contain both AR-positive and AR-negative NE cells (Nakada et al. 1993); however, a prevalence of AR-negative NE cells has been reported in more advanced disease (Krijnen et al. 1993, Bonkhoff 1998). NE cells in prostate cancer appear to be distinct from NE cells in benign prostate and may result from the transdifferentiation of epithelial cells (Nelson et al. 2007). Several varieties of prostatic NED have been described, including highly malignant NE cells of the small-cell carcinoma and carcinoid tumors. In prostatic adenocarcinoma, individual NE cells are surrounded by small foci of epithelial cells (Nelson et al. 2007). In general, NE differentiation is accompanied by a worse prognosis and resistance to therapy (Fixemer et al. 2002). The NE differentiation marker chromogranin A (CgA) is considered to be a marker of advanced disease (Berruti et al. 2010), although the value of NE markers in predicting disease progression is not uniformly accepted (Jeetle et al. 2012).

Various inflammatory cytokines have been reported to induce NED in prostate cancer cells (Kim et al. 2004), and in turn, NED has been shown to cause the release of various cytokines that stimulated prostate cancer progression (Nelson et al. 2007). Earlier studies have shown that the COX-2 inhibitor NS-398 increased MIF production and stimulated NED in prostate cancer cells (Meyer-Siegler 2001). However, the link between NED and MIF secretion had not been established. Now, Tawadros et al. (2013), using androgen-dependent LNCaP prostate cancer cells as a model, show that NED caused by either cAMP treatment or androgen deprivation, a standard therapy for prostate cancer, results in an increase in extracellular MIF secretion but a decrease in intracellular MIF protein and transcription levels. Significantly, extracellular MIF increase did not affect PSA levels, but yet resulted in increased proliferation. Since PSA expression is known to be AR regulated, this result indicates that the tumor-enhancing effects of MIF are AR independent. This result is important, since LNCaP cells express an active AR and support the growing body of literature stating that PSA levels do not accurately reflect tumor progression. MIF is known to activate both Akt and ERK signaling pathways (Ohta et al. 2012), and in prostate cancer cell lines, these pathways have been found to mediate proliferation. These pathways can be activated by both AR-dependent and AR-independent mechanisms, and in this case, these are clearly AR independent. Since both pathways have also been shown to stimulate AR transcripational activity in prostate cancer cells, it is curious as to why they did not affect PSA expression in this case. It is likely that the AR is completely bypassed in NED, such that not only does it not affect proliferation, but it also does not get transactivated by common pathways. In short, Tawadros et al. demonstrate that the paracrine action of MIF, but not autocrine action, induced NED differentiation and stimulated cell proliferation mediated by both ERK and Akt phosphorylation.
The significance of this paper lies in its ability to link MIF release in chronic inflammation, as seen, for example, in prostatitis and other prostate diseases caused by infections, to the development of NED in prostate cancer cells. MIF action is mediated by the cytokine receptor CD74, which plays a role in antigen presentation (Beswick & Reyes 2009). MIF has been implicated in lethal bacterial sepsis and the mediation of effects of endotoxins released by Gram-negative bacteria (Calandra & Roger 2003). With the advent of studies showing a positive correlation between infections and prostate cancer (Taylor et al. 2005, Cheng et al. 2010), the role of MIF in prostate cancer is likely to increase in importance. The number of MIF inhibitors available today is clearly inadequate ( Ouertatani-Sakouhi et al. 2010, Fujita et al. 2012), but novel MIF inhibitors are being developed (Garai & Lorand 2009, Lugrin et al. 2010, Ouertatani-Sakouhi et al. 2009, Piette et al. 2009) and may in the future have a use in the chemoprevention of prostate cancer in men with prostatitis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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