Linking Inflammation and Neuroendocrine Differentiation – the role of macrophage migration inhibitory factor mediated signaling in prostate cancer

Commentary on "Release of macrophage migration inhibitory factor by neuroendocrine differentiated LNCaP cells sustains the proliferation and survival of prostate cancer cells"

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ABSTRACT: A new paper by Tawadros et al in Endocrine Related Cancers 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), is 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 demonstrated 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 and De Marzo 2004). Common anti-inflammatory drugs were found to lower levels of serum prostate specific antigen (PSA), a marker of prostate cancer progression (Chang, et al. 2010). Although no relation between 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 was lacking. In recent times, various inflammatory cytokines were found to mediate proliferation of prostate cancer cells, such as IL-6 (Dutt and Gao 2009), and the macrophage inhibitory cytokine gene (MIC-1) (Dubey, et al. 2012). Another important regulator of prostate cancer progression now appears to be Macrophage migration inhibitory factor (MIF), also known as glycosylation inhibiting factor (GIF), 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 (Girard, et al. 2012; Verjans, et al. 2009).
MIF’s role in prostate cancer development and progression is not unknown. As early as 1996, investigators showed that this gene may regulate prostate cancer metastasis (Meyer-Siegler and Hudson 1996). Another early study showed neuroendocrine differentiation (NED) and MIF expression by the COX-2 inhibitor NS-398 (Meyer-Siegler 2001). MIF’s effect 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 in the Feb issue of *Endocrine Related Cancers* (Tawadros, et al. 2013). This group has for long been interested in the study of NED in prostate cancer (Tawadros, et al. 2005), and now show that MIF activates proliferation and survival through 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 and malignant prostate depends upon the androgen receptor (AR) for growth and survival; hence androgen deprivation therapy is a cornerstone of treatment for advanced, especially metastatic prostate cancer (Culig, et al. 2000; Ruizeveld de Winter, et al. 1994). The expression of the AR in NE tumors is slightly different. Benign and malignant prostatic tissue 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 (Bonkhoff 1998; Krijnen, et al. 1993). NE cells in prostate cancer appear to be distinct from NE cells in benign prostate and may result from 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 chromatogranin 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 was shown to cause the release of various cytokines that stimulated prostate cancer progression (Nelson et al. 2007). Earlier studies showed 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 (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, were found to mediate proliferation. These pathways can be activated by both AR-dependent and –independent
mechanisms, and in this case, is clearly AR-independent. Since both pathways have also been shown to stimulate AR transcriptional 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 in addition, AR is not transactivated by common pathways as well. In short, Tawadros et al demonstrate that 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 and Reyes 2009). MIF has been implicated in lethal bacterial sepsis and the mediation of effects of endotoxins released by gram negative bacteria (Calandra and Roger 2003). With the advent of studies showing a positive correlation between infections and prostate cancer (Cheng et al. 2010; Taylor, et al. 2005), the role of MIF in prostate cancer is likely to increase in importance. The number of MIF inhibitors available today is clearly inadequate (Fujita, et al. 2012; Ouertatani-Sakouhi, et al. 2010), but novel MIF inhibitors are being developed (Garai and Lorand 2009; Lugrin, et al. 2009; Ouertatani-Sakouhi, et al. 2009; Piette, et al. 2009), and may in the future have a use in chemoprevention of prostate cancer in men with prostatitis.

Declaration of interest:

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REFERENCES:


Piette C, Deprez M, Roger T, Noel A, Foidart JM & Munaut C 2009 The dexamethasone-induced inhibition of proliferation, migration, and invasion in glioma cell lines is antagonized by macrophage migration inhibitory factor (MIF) and can be enhanced by specific MIF inhibitors. *J Biol Chem* **284** 32483-32492.


