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.

Key Words

- ▶ prostate cancer
- ▶ neuroendocrine differentiation
- ▶ macrophage migration inhibitory factor
- ▶ prostatitis
- ▶ inflammation

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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 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 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.* 2009, 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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References

- Berruti A, Bollito E, Cracco CM, Volante M, Ciccone G, Porpiglia F, Papotti M, Scarpa RM & Dogliotti L 2010 The prognostic role of immunohistochemical chromogranin a expression in prostate cancer patients is significantly modified by androgen-deprivation therapy. *Prostate* **70** 718–726. (doi:10.1002/pros.21104)
- Beswick EJ & Reyes VE 2009 CD74 in antigen presentation, inflammation, and cancers of the gastrointestinal tract. *World Journal of Gastroenterology* **15** 2855–2861. (doi:10.3748/wjg.15.2855)
- Bonkhoff H 1998 Neuroendocrine cells in benign and malignant prostate tissue: morphogenesis, proliferation, and androgen receptor status. *Prostate. Supplement* **8** 18–22. (doi:10.1002/(SICI)1097-0045(1998)8+<18::AID-PROS4>3.0.CO;2-C)
- Calandra T & Roger T 2003 Macrophage migration inhibitory factor: a regulator of innate immunity. *Nature Reviews. Immunology* **3** 791–800. (doi:10.1038/nri1200)
- Chang SL, Harshman LC & Presti JC, Jr 2010 Impact of common medications on serum total prostate-specific antigen levels: analysis of the National Health and Nutrition Examination Survey. *Journal of Clinical Oncology* **28** 3951–3957. (doi:10.1200/JCO.2009.27.9406)
- Cheng I, Witte JS, Jacobsen SJ, Haque R, Quinn VP, Quesenberry CP, Caan BJ & Van Den Eeden SK 2010 Prostatitis, sexually transmitted diseases, and prostate cancer: the California Men's Health Study. *PLoS ONE* **5** e8736. (doi:10.1371/journal.pone.0008736)
- Culig Z, Hobisch A, Bartsch G & Klocker H 2000 Androgen receptor – an update of mechanisms of action in prostate cancer. *Urological Research* **28** 211–219. (doi:10.1007/s002400000111)
- Daniels NA, Chen YH & Bent S 2009 Antibiotic and anti-inflammatory use and the risk of prostate cancer. *BMC Research Notes* **2** 57. (doi:10.1186/1756-0500-2-57)
- Dennis LK, Lynch CF & Torner JC 2002 Epidemiologic association between prostatitis and prostate cancer. *Urology* **60** 78–83. (doi:10.1016/S0090-4295(02)01637-0)
- Dubey S, Vanveldhuizen P, Holzbeierlein J, Tawfik O, Thrasher JB & Karan D 2012 Inflammation-associated regulation of the macrophage inhibitory cytokine (MIC-1) gene in prostate cancer. *Oncology Letters* **3** 1166–1170.
- Dutt SS & Gao AC 2009 Molecular mechanisms of castration-resistant prostate cancer progression. *Future Oncology* **5** 1403–1413. (doi:10.2217/fon.09.117)
- Fixemer T, Remberger K & Bonkhoff H 2002 Apoptosis resistance of neuroendocrine phenotypes in prostatic adenocarcinoma. *Prostate* **53** 118–123. (doi:10.1002/pros.10133)
- Fujita Y, Islam R, Sakai K, Kaneda H, Kudo K, Tamura D, Aomatsu K, Nagai T, Kimura H, Matsumoto K *et al.* 2012 Aza-derivatives of resveratrol are potent macrophage migration inhibitory factor inhibitors. *Investigational New Drugs* **30** 1878–1886. (doi:10.1007/s10637-011-9749-7)
- Garai J & Lorand T 2009 Macrophage migration inhibitory factor (MIF) tautomerase inhibitors as potential novel anti-inflammatory agents: current developments. *Current Medicinal Chemistry* **16** 1091–1114. (doi:10.2174/092986709787581842)
- Girard E, Strathdee C, Trueblood E & Queva C 2012 Macrophage migration inhibitory factor produced by the tumour stroma but not by tumour cells regulates angiogenesis in the B16-F10 melanoma model. *British Journal of Cancer* **107** 1498–1505. (doi:10.1038/bjc.2012.392)
- Jeetle SS, Fisher G, Yang ZH, Stankiewicz E, Moller H, Cooper CS, Cuzick J, Berney DM & Trans-Atlantic Prostate G 2012 Neuroendocrine differentiation does not have independent prognostic value in conservatively treated prostate cancer. *Virchows Archiv* **461** 103–107. (doi:10.1007/s00428-012-1259-2)
- Kim J, Adam RM, Solomon KR & Freeman MR 2004 Involvement of cholesterol-rich lipid rafts in interleukin-6-induced neuroendocrine differentiation of LNCaP prostate cancer cells. *Endocrinology* **145** 613–619. (doi:10.1210/en.2003-0772)
- Krijnen JL, Janssen PJ, Ruizeveld de Winter JA, van Krimpen H, Schroder FH & van der Kwast TH 1993 Do neuroendocrine cells in human prostate cancer express androgen receptor? *Histochemistry* **100** 393–398. (doi:10.1007/BF00268938)
- Lugrin J, Ding XC, Le Roy D, Chanson AL, Sweep FC, Calandra T & Roger T 2009 Histone deacetylase inhibitors repress macrophage migration inhibitory factor (MIF) expression by targeting MIF gene transcription through a local chromatin deacetylation. *Biochimica et Biophysica Acta* **1793** 1749–1758. (doi:10.1016/j.bbamer.2009.09.007)
- Meyer-Siegler K 2001 COX-2 specific inhibitor, NS-398, increases macrophage migration inhibitory factor expression and induces neuroendocrine differentiation in C4-2b prostate cancer cells. *Molecular Medicine* **7** 850–860.
- Meyer-Siegler K & Hudson PB 1996 Enhanced expression of macrophage migration inhibitory factor in prostatic adenocarcinoma metastases. *Urology* **48** 448–452. (doi:10.1016/S0090-4295(96)00207-5)
- Meyer-Siegler KL, Iczkowski KA, Leng L, Bucala R & Vera PL 2006 Inhibition of macrophage migration inhibitory factor or its receptor (CD74) attenuates growth and invasion of DU-145 prostate cancer cells. *Journal of Immunology* **177** 8730–8739.
- Nakada SY, di Sant'Agnese PA, Moynes RA, Hiipakka RA, Liao S, Cockett AT & Abrahamsson PA 1993 The androgen receptor status of neuroendocrine cells in human benign and malignant prostatic tissue. *Cancer Research* **53** 1967–1970.
- Nelson EC, Cambio AJ, Yang JC, Ok JH, Lara PN, Jr & Evans CP 2007 Clinical implications of neuroendocrine differentiation in prostate cancer. *Prostate Cancer and Prostatic Diseases* **10** 6–14. (doi:10.1038/sj.pcan.4500922)

- Nishihira J, Ishibashi T, Fukushima T, Sun B, Sato Y & Todo S 2003 Macrophage migration inhibitory factor (MIF): Its potential role in tumor growth and tumor-associated angiogenesis. *Annals of the New York Academy of Sciences* **995** 171–182. (doi:10.1111/j.1749-6632.2003.tb03220.x)
- Ohta S, Misawa A, Fukaya R, Inoue S, Kanemura Y, Okano H, Kawakami Y & Toda M 2012 Macrophage migration inhibitory factor (MIF) promotes cell survival and proliferation of neural stem/progenitor cells. *Journal of Cell Science* **125** 3210–3220. (doi:10.1242/jcs.102210)
- Ouertatani-Sakouhi H, El-Turk F, Fauvet B, Roger T, Le Roy D, Karpinar DP, Leng L, Bucala R, Zweckstetter M, Calandra T *et al.* 2009 A new class of isothiocyanate-based irreversible inhibitors of macrophage migration inhibitory factor. *Biochemistry* **48** 9858–9870. (doi:10.1021/bi900957e)
- Ouertatani-Sakouhi H, El-Turk F, Fauvet B, Cho MK, Pinar Karpinar D, Le Roy D, Dewor M, Roger T, Bernhagen J, Calandra T *et al.* 2010 Identification and characterization of novel classes of macrophage migration inhibitory factor (MIF) inhibitors with distinct mechanisms of action. *Journal of Biological Chemistry* **285** 26581–26598. (doi:10.1074/jbc.M110.113951)
- 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. *Journal of Biological Chemistry* **284** 32483–32492. (doi:10.1074/jbc.M109.014589)
- Platz EA & De Marzo AM 2004 Epidemiology of inflammation and prostate cancer. *Journal of Urology* **171** S36–S40. (doi:10.1097/01.ju.0000108131.43160.77)
- Pruthi RS, Derksen JE, Moore D, Carson CC, Grigson G, Watkins C & Wallen E 2006 Phase II trial of celecoxib in prostate-specific antigen recurrent prostate cancer after definitive radiation therapy or radical prostatectomy. *Clinical Cancer Research* **12** 2172–2177. (doi:10.1158/1078-0432.CCR-05-2067)
- Roberts RO, Bergstralh EJ, Bass SE, Lieber MM & Jacobsen SJ 2004 Prostatitis as a risk factor for prostate cancer. *Epidemiology* **15** 93–99. (doi:10.1097/01.ede.0000101022.38330.7c)
- Ruizeveld de Winter JA, Janssen PJ, Sleddens HM, Verleun-Mooijman MC, Trapman J, Brinkmann AO, Santerse AB, Schroder FH & van der Kwast TH 1994 Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. *American Journal of Pathology* **144** 735–746.
- Tawadros T, Martin D, Abderrahmani A, Leisinger HJ, Waerber G & Haefliger JA 2005 IB1/JIP-1 controls JNK activation and increased during prostatic LNCaP cells neuroendocrine differentiation. *Cellular Signalling* **17** 929–939. (doi:10.1016/j.cellsig.2004.11.013)
- Tawadros T, Alonso F, Jichlinski P, Clarke N, Calandra T, Haefliger JA & Roger T 2013 Release of macrophage migration inhibitory factor by neuroendocrine-differentiated LNCaP cells sustains the proliferation and survival of prostate cancer cells. *Endocrine-Related Cancer* **20** 137–149. (doi:10.1530/ERC-12-0286)
- Taylor ML, Mainous AG, III & Wells BJ 2005 Prostate cancer and sexually transmitted diseases: a meta-analysis. *Family Medicine* **37** 506–512.
- Verjans E, Noetzel E, Bektas N, Schutz AK, Lue H, Lennartz B, Hartmann A, Dahl E & Bernhagen J 2009 Dual role of macrophage migration inhibitory factor (MIF) in human breast cancer. *BMC Cancer* **9** 230. (doi:10.1186/1471-2407-9-230)

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