Q J Med 2010; **103**:831–836
doi:10.1093/qjmed/hcq148 Advance Access Publication 30 August 2010

Review

QJM

Inflammation and cancer: macrophage migration inhibitory factor (MIF)—the potential missing link

H. CONROY, L. MAWHINNEY and S. C. DONNELLY

From the Conway Institute for Biomolecular and Biomedical Research, School of Medicine and Medical Science, University College Dublin, Dublin 4, Ireland

Address correspondence to: Prof. S. C. Donnelly, Medicine & Therapeutics, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland. email: seamas.donnelly@ucd.ie

Summary

Macrophage migration inhibitory factor (MIF) was the original cytokine, described almost 50 years ago and has since been revealed to be an important player in pro-inflammatory diseases. Recent work using MIF mouse models has revealed new roles for MIF. In this review, we present an increasing body of evidence implicating the key pro-inflammatory cytokine MIF in specific biological activities related directly to cancer growth or contributing towards a microenvironment favouring cancer progression.

Introduction

Historically, the association between inflammation and cancer has been well recognized. In the 1970s, serum derived from BCG-infected endotoxin-treated mice was shown to induce significant necrosis in sarcoma tumour.[1] This active circulating cytokine was identified and consequently called tumour necrosis factor (TNF). More recently, a number of chronic inflammatory diseases have been shown to be associated with a variety of cancers (Table 1). With inflammation known to contribute to cancer development and progression, investigating the association between these two processes has never been more important. Macrophage migration inhibitory factor (MIF) displays a number of functions which provide a direct link between the processes of inflammation and tumour growth.

MIF was one of the first cytokines to be described almost 50 years ago and extensive studies since have revealed its central role in innate and adaptive immunity. More recently, the ability of this cytokine to support tumour progression has become clear and has revealed MIF as a potential target for anti-cancer therapies.

MIF was originally identified as a T-cell-derived factor responsible for the inhibition of macrophage migration in experiments designed to characterize delayed-type hypersensitivity.[2,3] The molecule is expressed by a variety of cells including eosinophils,[4] epithelial cells,[5] endothelial cells,[6] lymphocytes[7] and macrophage[8] and so, predictably, displays a wide range of activities. *In vivo* stimulation with endotoxin promotes secretion of MIF from pools of stored protein within the cell allowing immediate amplification of the inflammatory response. Studies showing that MIF-specific blocking antibodies could attenuate endotoxic shock confirmed the critical role that MIF plays in innate immunity.[9]

The crystal structure of MIF revealed the active form to be a 37.5 kDa homotrimer with novel protein folds that defined a new structural

Table 1 Chronic inflammatory conditions associated with enhanced risk for specific cancers

Inflammatory condition	Corresponding cancer
Barrett's oesophagus	Eosophageal cancer[48]
Helicobacter pylori infection	Gastric cancer[49]
Inflammatory bowel disease	Bowel cancer[50]
Hepatitis B or C	Hepatocellular carcinoma[51]
Obesity-related inflammation	Liver cancer[52]
Tobacco-particulate induced inflammation	Lung cancer[53]
Coeliac disease	Lymphoma[54]
Rheumatoid arthritis	Lymphoma[55]
Schistosomiasis	Bladder cancer[56]
Osteomyelitis	Sarcoma[57]

superfamily.[10,11] In addition to its distinctive structure, MIF possesses a unique enzymatic activity revealed through its structural homology to several bacterial enzymes. This tautomerase activity mediated by an N-terminal proline residue, allows MIF to catalyse the conversion of non-physiological substrates D-dopachrome or L-dopachrome methyl esters to their indole derivatives. As yet, no human physiological substrates for MIF tautomerase have been identified.

The discovery that MIF was secreted from corticotrophic pituitary cells led to its classification as a hormone as well as a cytokine. Its release coincides with, and is induced by adrenocorticotrophic hormone and its ability to override the anti-inflammatory effects of this hormone suggested an inbuilt regulatory mechanism.[9] This ability to promote inflammation while hindering the anti-inflammatory effects of glucocorticoids was implicated in the pathogenesis of acute respiratory distress syndrome (ARDS).[12] Direct association between MIF expression levels and degrees of disease pathogenesis in a number of inflammatory diseases was revealed through analysis of genetic variation within the MIF gene.[13–15] Allelic variation within a repeat region found upstream of the MIF promoter, determines efficiency of expression of the protein. Individuals carrying five copies of the CATT repeat element were found to display lower MIF levels, with those possessing increasing numbers of repeats (6, 7 or 8) having a corresponding increase in expression. In cystic fibrosis patients, this increase in MIF production associated with carrying the 6 and 7 repeat variants was associated with enhanced end-organ injury. Rheumatoid arthritis patients carrying the 6 and 7 repeat variants had both higher basal levels of MIF and higher levels following stimulation with forskolin or serum. The higher levels of MIF associated with this particular variant also correlated with progressive disease.[16] In relation to malignant diseases, individuals carrying the seven-repeat allele were also found to have an increased incidence of prostate cancer.[17] MIF biological activity has also been implicated in the pathogenesis of atherosclerosis and abdominal aortic aneurysm.[18] In the context of atherosclerosis, MIF has also been identified as a non-cognate receptor of CXCR2 and CXCR4 and has functional chemokine activity in evolving atherosclerosis mediating monocyte arrest and the formation of plaques.[19] Additionally, as part of this disease process MIF can induce the CXCR ligand, Interleukin (IL)-8 and regulators of macrophage infiltration ICAM-1 and CD44, confirming its relevance in this disease.[20]

Mounting evidence suggests that inflammation is closely associated with many types of cancer.[21] Inflammatory pathways designed to defend against infection and injury can promote an environment which favours tumour growth and metastasis. Chronic inflammatory conditions and infections have been directly linked to specific cancers, see Table 1. Supporting this observation, treatment with non-steroidal anti-inflammatory drugs has been shown to reduce the risk of developing colon cancer.[22] Consequently, there is heightened interest both within academia and industry, to define key regulatory events within the inflammatory process which predispose individuals to enhanced cancer risk. This would provide the rational for significant investment in these high-value therapeutic targets for drug development.

MIF and cancer

MIF's unique biological activities have the potential to contribute to an *in vivo* microenvironment favouring tumour growth and invasiveness. These functional activities include: tumour suppressor downregulation, COX-2 and PGE2 upregulation, potent induction of angiogenesis and enhanced tumour growth, proliferation and invasiveness (summarized in Table 2).

MIF and the tumour suppressor p53

MIF demonstrates a direct link between inflammation and tumourigenesis. As well as its established role in inflammation, MIF directly promotes tumourigenesis by inhibiting p53 accumulation. P53 is a classic tumour suppressor gene that can promote cell cycle arrest and apoptosis in response to DNA damage. Absence or downregulation of p53

Table 2 MIF biological activities which favour tumour pathogenesis

MIF functional activities	Role in tumourigenesis
P53 inhibition	Accumulation of mutation Inhibition of apoptosis Proliferation of cells
Sustained ERK activation	Promotes invasion Inhibits cell death
COX-2/PGE-2 induction	Tumour Growth Viability Metastasis
Endothelial cell proliferation and differentiation	Promotes angiogenesis

interferes with this important checkpoint for maintaining genetic stability and allows cell survival and proliferation despite the potential accumulation of mutations. Functional screens carried out by Hudson *et al*.[23] to identify cDNAs capable of negatively regulating p53 identified MIF. Over-expression of MIF down regulated p53 levels and suppressed nuclear localization, thereby prohibiting its transcriptional activity. Most importantly, MIF-suppressed p53-dependent senescence in primary mouse embryonic fibroblasts (MEFs) and inhibited apoptosis induced by serum starvation. Furthermore, in a separate study, a role for MIF in suppression of activation-induced cell death (AICD) was identified using MIF null mice.[24] Lipopolysaccharide administration produced increased macrophage AICD and an associated decrease in inflammatory cytokines in MIF null mice compared to wild-type mice. This again points to the key role MIF plays in amplifying inflammation, as well as promoting cell survival.

An important event in many cancer cells is the activation of endogenous oncogenes such as the prototypic oncogene Ras. Ras is a GTP-ase signalling molecule capable of promoting cell proliferation and malignancy. MIF-deficient cells were found to be resistant to p53-associated Ras oncogenic transformation which is mediated downstream through Rb and E2F. Transformation induced by Ras was restored upon deletion of p53.[25,26]

MIF receptor signalling and tumour pathogenesis

MIF protein is found to be over-expressed in a number of cancers and expression levels have been found to correlate with disease severity and invasiveness. For example, in a mouse model of intestinal cancer, MIF expression was found to be increased in tumour tissue relative to normal intestine. In addition, MIF added exogenously to a human colon adenocarcinoma cell line promoted anchorage-independent growth of the cells and inhibited cell death.[27]As well as its interactions with tumour suppressors, MIF promotes cellular proliferation through activation of members of the MAPK family. MIF signalling through CD74 promotes sustained ERK activation. The importance of this activity is clear when you consider that this is the main outcome of mutations in Ras which occur in a third of human tumours.[28] MIF stimulates phosphorylation of p42/p44 MAPK through PKA. This results in downstream activation of cPLA2 and release of the prostaglandin precursor arachadonic acid, a potential substrate for COX-2 now known to be induced as an important element of p53 inhibition by MIF. Sustained ERK activation is also observed in the PC12 model of neuronal differentiation, again suggesting a role for MIF in cell cycle progression.[29]

While CD74 mediates MIF binding, a co-receptor, CD44, is required for ERK 1 and 2 phosphorylation.[30,31] Blocking of MIF or MIF signalling, by blocking CD74 attenutates prostate cancer invasiveness.[32] Conversely, activation of CD44 promotes breast cancer cell invasion.[33] CD44+ breast cancer cells with low or undetectable CD24 have been found to be more tumourigenic and have a characteristic 'invasiveness gene signature'.[34] Studies have also shown that CD44-positive prostate cancer and breast cancer cell lines demonstrate rapid adhesion to bone marrow endothelial cells which can be blocked by neutralizing CD44 antibody.[35] B lymphocytes that accumulate in chronic lymphocytic leukaemia have been found to have high expression of CD74 and stimulation of these cells with MIF induces anti-apoptotic Bcl-2 and promotes survival through an IL-8-dependent mechanism.[36] Blocking MIF signalling in this context decreases using anti-CD74 antibodies decreases cell survival.

MIF, hypoxia and angiogenesis

Hypoxia is very often associated with the tumour micro-environment. These hypoxic conditions in turn have been found to induce in tumours expression of specific patterns of genes which confer a survival advantage on cancer cells allowing tumour growth and spread in this environment. The master transcription factor HIF1α (hypoxia inducible factor) binds to HREs (hypoxia response elements) in the promoter of its target genes to activate their expression.[37] These targets include pro-invasive and pro-angiogenic genes such as

LOX, CTG[38] and Vascular endothelial growth factor (VEGF).[39,40] Simultaneously, HIF1α negatively regulates anti-angiogenic targets such as thrombospondin.[41] MIF is a direct transcriptional target of HIF-1α and, more importantly, loss of MIF results in inefficient HIF-1α stabilization induced by hypoxia.[42] MIF expression has been found to be up-regulated during hypoxia, with a HRE found in the 5′Untranslated Region of the gene.[43,44] MIF also supports tumour growth in a hypoxic environment through significantly enhancing angiogenesis. Through the activation of MAP kinases MIF enhances the differentiation of endothelial cells to blood vessels.[45,46] In human breast cancer cells, MIF over-expression correlates with IL-8 and VEGF expression associated with angiogenesis.[47]

MIF, enzymatic activity and tumour progression

A unique functional characteristic of MIF, which sets it apart from other cytokines is its enzymatic activity.[58] The precise role of this novel tautomerase enzymatic activity has not been fully defined. In relation to cancer pathogenesis, investigators have sought to define this enzymatic activity by both utilizing catalytically inactive recombinant proteins *in vitro* and in animal models by using a transgenic mouse expressing enzymatically inactive MIF.[59] The P1G mouse expresses a mutated MIF where a terminal proline has been replaced by a glycine resulting in specific loss of this enzymatic activity. While binding of MIF to CD74 and JAB1 was not significantly reduced, the mutation eliminated MIF enzymatic activity and intriguingly impaired specific MIF biological activity. With regard to cancer animal models, chemically induced skin tumours are less effectively induced in P1G mutant mice. This work suggests that apart from a potential role for the enzymatic activity, the tautomerase site is also required for important protein–protein interactions.

Small molecular weight inhibitors of MIF tautomerase activity have also been used to dissect out the importance of this unique activity in cancer pathogenesis. ISO-1 is one such inhibitor designed to fit into the catalytic site of MIF.[60] Using colorectal cancer as a model where serum concentration of MIF have been shown to correlate with increased risk of metastasis to the liver, *in vivo* treatment of colon carcinoma-bearing mice with ISO-1 results in decreased tumour volume, reduced angiogenesis and less liver metastasis.[61] ISO-1 has also been shown to restore dexamethasone sensitivity in glioma cells which inhibits MIF-induced promotion of migration and invasion of the cells via MAP kinases. Both enzyme kinetic studies and *in vivo* toxicity studies suggest a limited role for ISO-1 in human studies. However, our expanding knowledge of this novel enzymatic activity in human disease provides the rationale for the further development of more refined small molecular weight enzymatic inhibitors targeting specifically this novel activity.

It is our conjecture that individuals who are genetically predisposed to exhibit chronic injurious inflammation are at enhanced risk of cancer progression. Our expanding knowledge of MIF biology now includes a greater understanding of its ability to both directly promote tumour growth and indirectly create a nurturing local tumour microenvironment, as well as insight into the genetic regulation of MIF expression. Increasingly, this evidence highlights MIF, as a prime therapeutic target in patients with augmented inflammatory responses that predispose to cancer development.

Conflict of interest: None declared.

References

1. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* 1975; **72**:3666–70.
2. Bloom BR, Bennett B. Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. *Science* 1966; **153**:80–2.
3. David JR. Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. *Proc Natl Acad Sci USA* 1966; **56**:72–7.
4. Rossi AG, Haslett C, Hirani N, Greening AP, Rahman I, Metz CN, *et al.* Human circulating eosinophils secrete macrophage migration inhibitory factor (MIF). Potential role in asthma. *J Clin Invest* 1998; **101**:2869–74.
5. Imamura K, Nishihira J, Suzuki M, Yasuda K, Sasaki S, Kusunoki Y, *et al.* Identification and immunohistochemical localization of macrophage migration inhibitory factor in human kidney. *Biochem Mol Biol Int* 1996; **40**:1233–42.
6. Nishihira J, Koyama Y, Mizue Y. Identification of macrophage migration inhibitory factor (MIF) in human vascular endothelial cells and its induction by lipopolysaccharide. *Cytokine* 1998; **10**:199–205.
7. Bacher M, Metz CN, Calandra T, Mayer K, Chesney J, Lohoff M, *et al.* An essential regulatory role for macrophage migration inhibitory factor in T-cell activation. *Proc Natl Acad Sci USA* 1996; **93**:7849–54.
8. Calandra T, Bernhagen J, Mitchell RA, Bucala R. The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor. *J Exp Med* 1994; **179**:1895–902.
9. Bernhagen J, Calandra T, Mitchell RA, Martin SB, Tracey KJ, Voelter W, *et al.* MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. *Nature* 1993; **365**:756–9.

10. Sun HW, Bernhagen J, Bucala R, Lolis E. Crystal structure at 2.6-A resolution of human macrophage migration inhibitory factor. *Proc Natl Acad Sci USA* 1996; **93**:5191–6.
11. Sun HW, Swope M, Cinquina C, Bedarkar S, Bernhagen J, Bucala R, *et al.* The subunit structure of human macrophage migration inhibitory factor: evidence for a trimer. *Protein Eng* 1996; **9**:631–5.
12. Donnelly SC, Haslett C, Reid PT, Grant IS, Wallace WA, Metz CN, *et al.* Regulatory role for macrophage migration inhibitory factor in acute respiratory distress syndrome. *Nat Med* 1997; **3**: 320–3.
13. Plant BJ, Gallagher CG, Bucala R, Baugh JA, Chappell S, Morgan L, *et al.* Cystic fibrosis, disease severity, and a macrophage migration inhibitory factor polymorphism. *Am J Respir Crit Care Med* 2005; **172**:1412–5.
14. Plant BJ, Ghani S, O'Mahony MJ, Morgan L, O'Connor CM, Morgan K, *et al.* Sarcoidosis and MIF gene polymorphism: a case-control study in an Irish population. *Eur Respir J* 2007; **29**:325–9.
15. Mizue Y, Ghani S, Leng L, McDonald C, Kong P, Baugh J, *et al.* Role for macrophage migration inhibitory factor in asthma. *Proc Natl Acad Sci USA* 2005; **102**:14410–5.
16. Baugh JA, Chitnis S, Donnelly SC, Monteiro J, Lin X, Plant BJ, *et al.* A functional promoter polymorphism in the macrophage migration inhibitory factor (MIF) gene associated with disease severity in rheumatoid arthritis. *Genes Immun* 2002; **3**:170–6.
17. Meyer-Siegler KL, Vera PL, Iczkowski KA, Bifulco C, Lee A, Gregersen PK, *et al.* Macrophage migration inhibitory factor (MIF) gene polymorphisms are associated with increased prostate cancer incidence. *Genes Immun* 2007; **8**:646–52.
18. Pan JH, Lindholt JS, Sukhova GK, Baugh JA, Henneberg EW, Bucala R, *et al.* Macrophage migration inhibitory factor is associated with aneurysmal expansion. *J Vasc Surg* 2003; **37**:628–35.
19. Bernhagen J, Krohn R, Lue H, Gregory JL, Zernecke A, Koenen RR, *et al.* MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. *Nat Med* 2007; **13**:587–96.
20. Verschuren L, Kooistra T, Bernhagen J, Voshol PJ, Ouwens DM, van Erk M, *et al.* MIF deficiency reduces chronic inflammation in white adipose tissue and impairs the development of insulin resistance, glucose intolerance, and associated atherosclerotic disease. *Circ Res* 2009; **105**:99–107.
21. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**:436–44.
22. Koehne CH, Dubois RN. COX-2 inhibition and colorectal cancer. *Semin Oncol* 2004; **31(2 Suppl 7)**:12–21.
23. Hudson JD, Shoaibi MA, Maestro R, Carnero A, Hannon GJ, Beach DH. A proinflammatory cytokine inhibits p53 tumor suppressor activity. *J Exp Med* 1999; **190**: 1375–82.
24. Mitchell RA, Liao H, Chesney J, Fingerle-Rowson G, Baugh J, David J, *et al.* Macrophage migration inhibitory factor (MIF) sustains macrophage proinflammatory function by inhibiting p53: regulatory role in the innate immune response. *Proc Natl Acad Sci USA* 2002; **99**:345–50.
25. Fingerle-Rowson G, Petrenko O, Metz CN, Forsthuber TG, Mitchell R, Huss R, *et al.* The p53-dependent effects of macrophage migration inhibitory factor revealed by gene targeting. *Proc Natl Acad Sci USA* 2003; **100**:9354–9.
26. Petrenko O, Fingerle-Rowson G, Peng T, Mitchell RA, Metz CN. Macrophage migration inhibitory factor deficiency is associated with altered cell growth and reduced susceptibility to Ras-mediated transformation. *J Biol Chem* 2003; **278**:11078–85.
27. Wilson JM, Coletta PL, Cuthbert RJ, Scott N, MacLennan K, Hawcroft G, *et al.* Macrophage migration inhibitory factor promotes intestinal tumorigenesis. *Gastroenterology* 2005; **129**:1485–503.
28. Kyriakis JM. Thinking outside the box about Ras. *J Biol Chem* 2009; **284**:10993–4.
29. Qui MS, Green SH. PC12 cell neuronal differentiation is associated with prolonged p21ras activity and consequent prolonged ERK activity. *Neuron* 1992; **9**:705–17.
30. Shi X, Leng L, Wang T, Wang W, Du X, Li J, *et al.* CD44 is the signaling component of the macrophage migration inhibitory factor-CD74 receptor complex. *Immunity* 2006; **25**:595–606.
31. Mitchell RA, Metz CN, Peng T, Bucala R. Sustained mitogen-activated protein kinase (MAPK) and cytoplasmic phospholipase A2 activation by macrophage migration inhibitory factor (MIF). Regulatory role in cell proliferation and glucocorticoid action. *J Biol Chem* 1999; **274**:18100–6.
32. Meyer-Siegler KL, Iczkowski KA, Leng L, Bucala R, Vera PL. Inhibition of macrophage migration inhibitory factor or its receptor (CD74) attenuates growth and invasion of DU-145 prostate cancer cells. *J Immunol* 2006; **177**:8730–9.
33. Bourguignon LY, Singleton PA, Zhu H, Diedrich F. Hyaluronan-mediated CD44 interaction with RhoGEF and Rho kinase promotes Grb2-associated binder-1 phosphorylation and phosphatidylinositol 3-kinase signaling leading to cytokine (macrophage-colony stimulating factor) production and breast tumor progression. *J Biol Chem* 2003; **278**:29420–34.
34. Liu R, Wang X, Chen GY, Dalerba P, Gurney A, Hoey T, *et al.* The prognostic role of a gene signature from tumorigenic breast-cancer cells. *N Engl J Med* 2007; **356**:217–226.
35. Draffin JE, McFarlane S, Hill A, Johnston PG, Waugh DJ. CD44 potentiates the adherence of metastatic prostate and breast cancer cells to bone marrow endothelial cells. *Cancer Res* 2004; **64**:5702–11.
36. Binsky I, Haran M, Starlets D, Gore Y, Lantner F, Harpaz N, *et al.* IL-8 secreted in a macrophage migration-inhibitory factor- and CD74-dependent manner regulates B cell chronic lymphocytic leukemia survival. *Proc Natl Acad Sci USA* 2007; **104**:13408–13.
37. Finger EC, Giaccia AJ. Hypoxia, inflammation, and the tumor microenvironment in metastatic disease. *Cancer Metastasis Rev* 2010; **29**:285–93.
38. Higgins DF, Biju MP, Akai Y, Wutz A, Johnson RS, Haase VH. Hypoxic induction of Ctgf is directly mediated by Hif-1. *Am J Physiol Renal Physiol* 2004; **287**:F1223–32.
39. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 1992; **359**:843–5.
40. Erler JT, Giaccia AJ. Lysyl oxidase mediates hypoxic control of metastasis. *Cancer Res* 2006; **66**:10238–41.
41. Laderoute KR, Alarcon RM, Brody MD, Calaoagan JM, Chen EY, Knapp AM, *et al.* Opposing effects of hypoxia on expression of the angiogenic inhibitor thrombospondin 1 and

the angiogenic inducer vascular endothelial growth factor. *Clin Cancer Res* 2000; **6**:2941–50.

42. Winner M, Koong AC, Rendon BE, Zundel W, Mitchell RA. Amplification of tumor hypoxic responses by macrophage migration inhibitory factor-dependent hypoxia-inducible factor stabilization. *Cancer Res* 2007; **67**:186–93.
43. Koong AC, Denko NC, Hudson KM, Schindler C, Swiersz L, Koch C, *et al.* Candidate genes for the hypoxic tumor phenotype. *Cancer Res* 2000; **60**:883–7.
44. Baugh JA, Gantier M, Li L, Byrne A, Buckley A, Donnelly SC. Dual regulation of macrophage migration inhibitory factor (MIF) expression in hypoxia by CREB and HIF-1. *Biochem Biophys Res Commun* 2006; **347**:895–903.
45. Amin MA, Volpert OV, Woods JM, Kumar P, Harlow LA, Koch AE. Migration inhibitory factor mediates angiogenesis via mitogen-activated protein kinase and phosphatidylinositol kinase. *Circ Res* 2003; **93**:321–9.
46. Chesney J, Metz C, Bacher M, Peng T, Meinhardt A, Bucala R. An essential role for macrophage migration inhibitory factor (MIF) in angiogenesis and the growth of a murine lymphoma. *Mol Med* 1999; **5**:181–91.
47. Xu X, Wang B, Ye C, Yao C, Lin Y, Huang X, *et al.* Overexpression of macrophage migration inhibitory factor induces angiogenesis in human breast cancer. *Cancer Lett* 2008; **261**:147–57.
48. Reid BJ, Li X, Galipeau PC, Vaughan TL. Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis. *Nat Rev Cancer* 2010; **10**:87–101.
49. Herrera V, Parsonnet J. Helicobacter pylori and gastric adenocarcinoma. *Clin Microbiol Infect* 2009; **15**:971–6.
50. Feagins LA, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. *Nat Rev Gastroenterol Hepatol* 2009; **6**:297–305.
51. Fung J, Lai CL, Yuen MF. Hepatitis B and C virus-related carcinogenesis. *Clin Microbiol Infect* 2009; **15**:964–70.
52. Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology* 2004; **127**(**5 Suppl 1**):S97–103.
53. Lee G, Walser TC, Dubinett SM. Chronic inflammation, chronic obstructive pulmonary disease, and lung cancer. *Curr Opin Pulm Med* 2009; **15**:303–7.
54. Catassi C, Bearzi I, Holmes GK. Association of celiac disease and intestinal lymphomas and other cancers. *Gastroenterology* 2005; **128**(**4 Suppl 1**):S79–86.
55. Symmons DP. Lymphoma and rheumatoid arthritis—again. *Rheumatology* 2007; **46**:1–2.
56. de Martel C, Franceschi S. Infections and cancer: established associations and new hypotheses. *Crit Rev Oncol Hematol* 2009; **70**:183–94.
57. Horvai A, Unni KK. Premalignant conditions of bone. *J Orthop Sci* 2006; **11**:412–23.
58. Rosengren E, Bucala R, Aman P, Jacobsson L, Odh G, Metz CN, *et al.* The immunoregulatory mediator macrophage migration inhibitory factor (MIF) catalyzes a tautomerization reaction. *Mol Med* 1996; **2**:143–9.
59. Fingerle-Rowson G, Kaleswarapu DR, Schlander C, Kabgani N, Brocks T, Reinart N, *et al.* A tautomerase-null macrophage migration-inhibitory factor (MIF) gene knock-in mouse model reveals that protein interactions and not enzymatic activity mediate MIF-dependent growth regulation. *Mol Cell Biol* 2009; **29**:1922–32.
60. Al-Abed Y, Dabideen D, Aljabari B, Valster A, Messmer D, Ochani M, *et al.* ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis. *J Biol Chem* 2005; **280**:36541–4.
61. He XX, Chen K, Yang J, Li XY, Gan HY, Liu CY, *et al.* Macrophage migration inhibitory factor promotes colorectal cancer. *Mol Med* 2009; **15**:1–10.