What can rheumatologists learn from translational cancer therapy?

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DOI:
10.1186/ar4203

arthritis research&therapy

COMMENTARY

What can rheumatologists learn from translational cancer therapy?

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Abstract

It is well established that an intimate connection exists between inflammation and neoplasia. Indeed, particular chronic infections and autoimmune processes giving rise to prolonged site-specific inflammation are known to increase the probability of the development of specific cancers. Molecular characterisation of these processes has revealed profound similarities in the specific molecules involved in persistence of inflammation and in both the primary induction of neoplastic processes and in specification of the preferred anatomic sites of metastatic spread. The therapeutic importance of these findings is underscored by the remarkable success in the treatment of autoimmune pathology using medications initially developed for use in oncology and this arena is one of considerable therapeutic promise for rheumatologists.

An intimate connection between inflammation and cancer has been proposed for decades based upon both biological similarities and clinical observation. Numerous autoimmune diseases are associated with neoplasia, with an elevated risk of lymphoma in Sjögren's syndrome [1] and rheumatoid arthritis [2], and gastrointestinal inflammation in Crohn's disease and ulcerative colitis is likewise associated with increased risk of intestinal neoplasia [3]. Inflammation induced by infectious organisms may also result in neoplasia, as exemplified by the association of *Helicobacter pylori* infection and gastric cancer, hepatitis C virus and hepatic cancer [4] and schistosomiasis and bladder cancer [5]. It has been estimated that 15% of malignancies may be caused by an underlying infection [6].

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One of the most fundamental biological similarities between inflammation and cancer is the presence of similar inflammatory cells in these processes, and on occasions these immune cells have been demonstrated to be essential for tumour progression. Mast cells, for example, are required for tumour growth in a model of pancreatic cancer [7] and macrophages promote invasive, metastatic behaviour in murine mammary cancer [8]. The importance of these cellular similarities is underscored by the observation that inhibition of tyrosine kinase activity with imatinib is an established therapeutic strategy in systemic mastocytosis [9] and chronic myeloid leukaemia [10], but has also been reported to be effective in rheumatoid arthritis [11-13]. Tumours frequently manipulate the host immune response - for example, by secreting chemokines to induce a tolerogenic cellular microenvironment - and may stimulate angiogenesis through elaboration of inflammatory cytokines [14]. As well as cells, inflammatory signalling molecules such as NF-kB are often shared between neoplastic and inflammatory conditions, and these molecules promote both processes. Thus, inactivation of this pathway in intestinal epithelial cells results in a direct reduction of tumour incidence, whereas its inactivation in myeloid cells, which cause inflammation, results in a reduction of pro-inflammatory cytokines and resultant decrease in tumour size [15]. Similarly, both NF-κB and STAT-3 signalling pathways have been strongly implicated in hepatoma development [16]. Further examples of the shared role of molecules in neoplasia and inflammatory arthritis include the Myc oncoprotein, which has also been shown to induce angiogenesis through the elaboration of IL-1β [17]. As well as this role in tumour vascularisation, this cytokine contributes to inflammation in rheumatoid arthritis, as indicated by the effects of IL-1β neutralisation in this disease [18]. Given the importance of the signalling pathway that operates through the mammalian target of rapamycin (mTOR) in both immune and neoplastic cells, attention is currently focussed on therapeutic approaches centred on this molecule for both autoimmune and neoplastic pathologies [19,20].

Suggestions of a causal role of inflammation in cancer emerge from the observation that the development of

neoplasia in response to inflammation is strongly associated with the chronicity and intensity of the inflammatory stimulus. Patients with high disease activity in rheumatoid arthritis thus have the highest chance of developing lymphoma [2]. Indeed, pro-inflammatory molecules produced within inflammatory lesions can themselves directly promote genomic instability, as exemplified by reactive oxygen and nitrogen species that result in DNA damage [21]. Early experiments demonstrated that culture with neutrophils elaborating reactive oxygen species endows fibroblasts with an ability to induce tumour development when transferred into mice [22]. Moreover, the rapid cell proliferation associated with inflammation results in further cellular susceptibility to DNA damage in an environment where, in addition, DNA repair processes are themselves compromised. Co-culture of activated neutrophils with human alveolar epithelial cells reveals that neutrophils and the hypochlorous acid that they produce can strongly inhibit nucleotide excision repair (NER) of damaged DNA and this effect can be abrogated by inhibiting production of hypochlorous acid [23]. Inflammatory cells, moreover, express tissue degradative enzymes and promote angiogenesis, processes that aid neoplastic cells to metastasise.

That inflammation itself can induce genetic mutation and thus predispose to neoplastic development is demonstrated by the spontaneous inflammatory bowel disease that develops in interleukin-10 deficient mice, since this is associated with a colonic mutation rate five times greater than wild-type mice, with a ten-fold increase in small deletions and insertions to DNA [24]. Indeed, mutations of p53 are found in both human inflammatory bowel disease [25] and rheumatoid synovium [26]. In addition to compromised p53 activity through mutation, this molecule can also be functionally inhibited by the pro-inflammatory molecule macrophage migration inhibitory factor [27], demonstrating another important means by which inflammation, if unchecked, can potentially induce dysregulated cellular proliferation.

The shared use of chemokine receptors in driving both tissue-specific inflammation and tissue-specific metastases of neoplastic cells has received increasing attention. Indeed, the chemokine receptors CXCR4 and CCR7 are expressed on breast cancer tumours and metastases, and their ligands highly expressed in the preferential metastatic sites [28]. Differential expression of chemokine receptors on different tumours and their ligands in metastatic sites explains the differential patterns of metastases, just as these molecules co-ordinate immune cell trafficking.

The extremely potent pro-inflammatory cytokine IL-23 demonstrates a further central connection between autoimmune disease and cancer. This cytokine is central to autoimmune inflammation and has been shown to play a fundamental role in spondyloarthropathy, for which it is a promising therapeutic target [29]. However, IL-23 is also expressed within the vast majority of human carcinomas, where it promotes inflammation and expression of degradative enzymes such as MMP9 [30]. In neoplastic settings, IL-23 inhibits protective anti-tumour immunity. In addition to IL-23, other pro-inflammatory cytokines have been demonstrated to be important in promoting neoplasia, with TNF, IL-1 and IL-6 playing key roles in ovarian cancer [31], and these molecules are established therapeutic targets that are neutralised in routine clinical practice for rheumatoid arthritis [18,32,33].

The intimate connection between inflammation and cancer has encouraged the use of anti-inflammatory agents to halt neoplastic development. Indeed, aspirin has been shown to reduce the incidence of cancer [34] and mice with deficiency in the COX enzymes that this drug targets have reduced skin tumorigenesis [35]. Indeed, the reduced incidence of gastrointestinal and gynaecological cancers in rheumatoid arthritis patients has been attributed to non-steroidal anti-inflammatory drug (NSAID) use [36]. Many chemotherapeutic agents are in clinical use not only for treatment of cancer, but also for immune-mediated inflammation, prime examples being cyclophosphamide and methotrexate. Moreover, modern biological agents are also efficacious in both settings. Thus, rituximab is used to treat haematological malignancy, being effective in follicular and mantle cell lymphoma and diffuse large B cell lymphoma [37], but also significantly improves clinical outcomes in rheumatoid arthritis [38]. Even TNF blockade, which some view as potentially facilitating oncogenesis, may also be viewed as protective against cancer development with recent studies conducted in renal cell and ovarian carcinoma [39-42].

Both inflammatory conditions [43] and cancer [44] are associated with extensive modulation of local stromal tissue, with elaboration of pro-inflammatory molecules. Moreover, the aforementioned mutations in p53 in rheumatoid synovium occur in islands of the intimal lining, most likely in type B fibroblast-like synoviocytes, and this is associated with elevated production of IL-6, the latter itself driving inflammation. Indeed, inflammation itself is worse in mice deficient in p53, which develop more severe collagen-induced arthritis [45]. Given the success of agents targeting cancer-associated stromal cells in general and the fibroblast markers FAP [46] and CD248 [47] in particular, targeting similar pathogenic stromal cells in immune-mediated inflammation has already shown [48], and is likely to continue to show, considerable promise.

Abbreviations

IL, interleukin; NF, nuclear factor; TNF tumour necrosis factor.

Competing interests
The authors declare that they have no competing interests.

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Published: 1 May 2013

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doi:10.1186/ar4203
Cite this article as: Sherlock JP, *et al*.: **What can rheumatologists learn from translational cancer therapy?** *Arthritis Research & Therapy* 2013, **15:**114.