

Inflammation and cancer: The role of the human neutrophil

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DATES:

Received: 02 July 2013

Revised: 12 Sep. 2013

Accepted: 12 Sep. 2013

KEYWORDS:

angiogenesis; chemokines;
cytokines; hydrogen peroxide;
proteinases; redox signalling;
reactive oxygen species

HOW TO CITE:

Anderson R, Tintinger GR,
Feldman C. Inflammation
and cancer: The role of the
human neutrophil. *S Afr J
Sci.* 2014;110(1/2), Art.
#2013-0207, 6 pages.
[http://dx.doi.org/10.1590/
sajs.2014/20130207](http://dx.doi.org/10.1590/sajs.2014/20130207)

Chronic inflammation of both infective and non-infective origin has been implicated in the aetiology of approximately 30% of all human epithelial malignancies. The primary carcinogens are reactive oxygen species (ROS) derived from activated, infiltrating cells of the innate immune system, especially neutrophils, which inflict oxidative damage on the DNA of bystander epithelial cells. The consequence is gene modifications which initiate cellular transformation. The process of tumourigenesis is exacerbated by the sustained generation of pro-proliferative ROS, as well as by the release of neutrophil-derived cytokines and proteases, all of which contribute to tumour promotion and progression. It is now well recognised that, in addition to inflammation causing cancer, many cancers per se induce an inflammatory response, with a high magnitude of neutrophil influx being indicative of a poor prognosis. In this setting, CXC chemokines produced by tumours not only promote neutrophil influx and hyperactivity, but also cause autocrine activation of the proliferation of the chemokine-producing tumour cells. These various mechanisms of inflammation-mediated tumourigenesis are the primary focus of this review, together with a consideration of neutrophil-targeted anti-inflammatory strategies with potential as adjunctive cancer therapy.

Introduction

The link between cancer and inflammation was described 150 years ago by the distinguished German pathologist Rudolph Virchow.^{1,2} Based on epidemiological studies, it is now recognised that up to 30% of all cancers may have underlying inflammation-associated aetiology, triggered by chronic infection or other types of non-infective unresolved inflammation.³⁻⁶ In this setting, reactive oxygen and nitrogen species (ROS/RNS) released by activated phagocytes at sites of inflammation inflict oxidative damage on neighbouring bystander cells, especially epithelial cells, initiating tumourigenesis.^{7,8} Subsequent promotion/progression and metastasis involve not only ongoing oxidative stress, but also the release of pro-proliferative and pro-angiogenic/pro-metastatic, phagocyte-derived cytokines/chemokines and proteases.¹⁻¹⁷

Although inflammation is a major and primary cause of cancer, many cancers per se also activate an inflammatory response, resulting in infiltration by various types of myeloid cells of the innate immune system. These cells include neutrophils, monocytes/macrophages, dendritic cells, and so-called myeloid-derived suppressor cells of both granulocytic and monocytic origin.¹⁸⁻²³ Although this tumour-associated inflammatory response is potentially protective, at least in the case of neutrophils, monocytes/macrophages and dendritic cells,^{19,20} it may also contribute to tumour progression and metastasis through the mechanisms alluded to above.⁹

In this review, we focus on the pro-tumourigenic potential of the neutrophil, which, amongst other types of immune and inflammatory cells, is abundant in tumours, appearing to be an important, independent predictor of poor outcome in many,^{3,21} but not all, types²⁴ of malignancy. The major themes addressed here are the roles of neutrophil-derived/-associated ROS, chemokines/cytokines, proteinases and adhesion molecules in tumour initiation, promotion, progression and metastasis, as well as the potential role of anti-inflammatory strategies in cancer prevention and therapy.

Neutrophils and carcinogenesis

As described by Weitzman and Gordon in their seminal review⁷ and, more recently, by Knaapen et al.¹⁰, the propensity for cancers to develop at sites of inflammation is well recognised, the association being supported by compelling epidemiological and experimental evidence. Examples of inflammation-associated cancers, primarily epithelial, of both infective and non-infective origin are shown in Tables 1 and 2, respectively. In the setting of inflammation-associated cancer, phagocyte-derived ROS – produced and released extracellularly by infiltrating neutrophils – have been identified as the primary offenders.^{7,10} These indiscriminate, toxic agents are potent carcinogens, posing the potential hazard of oxidative damage to the DNA of bystander, host structural cells at sites of inflammation and resulting in the gene modifications which precede cellular transformation.

Convincing evidence demonstrating the carcinogenic potential of ROS was derived from experiments in which eukaryotic structural cells and lymphocytes were exposed to activated neutrophils, to cell-free enzymatic ROS-generating systems, or to the relatively stable, cell-permeant ROS hydrogen peroxide (H₂O₂) in vitro, which resulted in severe oxidative stress and damage to the genetic material of these cells.^{7,10} In all of these systems, direct oxidative damage to DNA appears to involve intracellular conversion of H₂O₂ to a highly potent and reactive ROS – hydroxyl radical – probably by Fenton-type mechanisms involving electron donation by heavy metals. The types of ROS-mediated damage include: (1) gross chromosomal damage (sister chromatid exchanges), (2) single- and double-DNA strand breaks and (3) oxidative damage to the bases in DNA.^{7,10} In the case of the latter, the signature of oxidative damage is conversion of guanosine to 8-hydroxydeoxyguanosine, although the other DNA bases are also vulnerable to oxidative damage.⁷ RNS produced predominantly by macrophages result in the formation of reactive aldehydes and malondialdehydes which also induce point mutations.⁸

In addition to the direct, DNA-damaging activities of phagocyte-derived ROS, these oxidants also inhibit the activities of several DNA repair enzymes, thereby exacerbating oxidative damage to genetic material.¹⁰ In this context, it is noteworthy that hypochlorous acid generated via the H₂O₂-dependent oxidation of chloride ions by myeloperoxidase (MPO), the neutrophil/monocyte primary granule enzyme, has been reported to interfere with the base excision repair enzyme poly (ADP-ribose) polymerase.²⁵ Other DNA repair enzymes which are susceptible to oxidative inactivation include the glycolase Ogg1 and topoisomerase II, which are inactivated by nitric oxide and H₂O₂, respectively, compromising repair of 8-hydroxydeoxyguanosine moieties and strand scission/ligation.^{10,26,27}

Table 1: Examples of inflammation-related malignancies of chronic infective origin

Type of malignancy	Associated infective agent
Squamous cell carcinoma of the bone, sinuses and skin	Chronic osteomyelitis most commonly caused by <i>Staphylococcus aureus</i>
Urinary bladder cancer	<i>Schistosoma haematobium</i>
Ovarian cancer	Pelvic inflammatory disease most commonly caused by <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i>
Gastric cancer	Gastritis caused by <i>Helicobacter pylori</i>
MALT lymphoma	<i>Helicobacter pylori</i>
Lung carcinomas	Chronic and recurrent pulmonary infection as a result of various bacterial pathogens
Testicular cancer	Orchitis caused by mumps virus
Hepatocellular carcinoma	Hepatitis viruses B and C
Cervical cancer	Human papilloma virus
Kaposi's sarcoma	Human herpes virus type 8

Sources¹⁻⁹

Table 2: Examples of inflammation-related malignancies of chronic non-infective origin

Type of malignancy	Associated condition
Colon carcinomas	Inflammatory bowel disease (Crohn's disease, colitis)
Urinary bladder cancer	Long-term indwelling catheters, stones
Gall bladder cancer	Chronic cholecystitis, cholelithiasis
Oesophageal squamous cell carcinoma and adenocarcinoma	Chronic exposure to chemical irritants and acid reflux oesophagitis, respectively
Lung carcinomas	Cigarette smoking, pulmonary fibrosis, sarcoidosis
Mesothelioma	Asbestos inhalation
Head and neck cancer	Cigarette smoking
Skin cancer (basal cell/squamous cell carcinoma, melanoma)	Exposure to sunlight

Sources¹⁻⁹

Clearly, ROS-mediated direct damage to DNA, together with oxidative dysfunction of DNA repair enzymes, predisposes to gene modifications,

which, particularly in the case of mutations to tumour suppressor and promoter genes, may lead to cellular transformation. However, these mechanisms are not the only ones by which phagocyte-derived ROS contribute to carcinogenesis. Other mechanisms include: (1) oxidative conversion of pre-carcinogenic chemicals/xenobiotics to complete carcinogens^{10,28}, (2) redox activation of intracellular signalling mechanisms, which not only promote aberrant cellular proliferation, but also intensify inflammation-related oxidative stress²⁹⁻³⁴ and (3) oxidative suppression of the proliferative activity of anti-tumour T lymphocytes^{35,36}. In addition to these mechanisms, several neutrophil-derived chemokines/cytokines, proteinases and adhesion molecules also contribute to tumourigenesis via their pro-proliferative, pro-angiogenic and pro-metastatic activities.

Neutrophil-mediated oxidative activation of pre-carcinogens

Neutrophil-derived ROS, specifically those generated by the MPO/H₂O₂/halide system, have been implicated in the transformation to carcinogens of chemical pollutants generated by industrial, motor vehicle and household combustive processes, as well as those present in cigarette smoke.¹⁰ Examples of the former include aromatic and heterocyclic amines, especially polycyclic aromatic hydrocarbons, while benzo(a)pyrene in cigarette smoke undergoes oxidative conversion to BPDE (bay-region diol epoxides), which is mutagenic via formation of covalent adducts with guanine.¹⁰ In addition, MPO-derived ROS have been reported to convert the anti-cancer drug etoposide to its potentially mutagenic phenoxy radical, which may explain the increased frequency of secondary myeloid leukaemia in cancer patients treated with this agent.²⁸

Redox activation of cellular proliferation

Unlike other ROS (such as superoxide anion, singlet molecular oxygen, hydroxyl radical and hypochlorous acid), H₂O₂ – because of its relative stability, cell permeability and ability to target proteins – can function efficiently as an intracellular signalling molecule.²⁹⁻³¹ Indeed, it is well established that H₂O₂ can modulate cellular differentiation, proliferation, survival and synthesis of inflammatory mediators via the oxidative modification of key cysteine residues in various enzymes, including phosphatases and kinases, especially mitogen-activated protein kinases (MAPKs), as well as transcription factors.²⁹⁻³² Under controlled conditions, H₂O₂ generated intracellularly in various types of cells by the ubiquitous, stringently regulated Nox (NADPH oxidase) family of enzymes, contributes positively to the maintenance of cellular homeostasis.²⁹⁻³² However, when structural cells, especially epithelial cells, are subjected to intense oxidative stress, whether directly as a consequence of protracted activation of Nox enzymes or indirectly because of influx of extracellular H₂O₂ as a result of proximity to activated phagocytes, or both, then cell proliferation as a consequence of dysregulated intracellular signalling may ensue. Although disputed by those who believe that over-exposure to H₂O₂ is more likely to drive the cells into apoptosis,²⁹⁻³² this scenario is countered to some extent by the following lines of evidence from experimental sources: (1) exposure of a Barrett's oesophagus adenocarcinoma cell line to low concentrations of H₂O₂ resulted in cell proliferation which was associated with sequential activation of extracellular regulated kinase 2, MAPK, the transcription factor, nuclear factor kappa B (NFκB) and Nox 5-S³³; and (2) exposure of human oral cancer cells to the H₂O₂-producing microorganism *Enterococcus faecalis* resulted in catalase-inhibitable activation of the epidermal growth factor receptor and cell proliferation, underscoring the association between infection with this bacterial pathogen and oral carcinogenesis.³⁴

ROS-mediated inactivation of tumour-targeted T cells

Although H₂O₂ at low concentrations can trigger the proliferation of epithelial cells via intracellular, redox signalling mechanisms, at higher concentrations this ROS can also promote the oxidative inactivation of the protective activities of T lymphocytes.^{35,36} In the setting of murine models of experimental tumourigenesis, infiltrating phagocytes, most

notably a subset of activated neutrophils, have been found to inhibit the protective responses of tumour-targeted T-lymphocytes. The mechanism of immunosuppression involves intimate cell-cell contact mediated by the neutrophil $\beta 2$ -integrin Mac-1, exposing the T cells to high concentrations of neutrophil-derived H_2O_2 .^{35,36}

Neutrophil-derived cytokines in tumourigenesis

Although originally believed to have a very short lifespan and an extremely limited biosynthetic capacity, the survival time of neutrophils in the circulation of healthy humans has recently been reported to be 5.4 days.³⁷ Following extravasation to sites of infection, tissue injury or cancer, this time may be considerably longer because of exposure to anti-apoptotic cytokines, especially granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor (GM-CSF).³⁸ Extended survival of neutrophils is associated with acquisition of the capacity, albeit limited, to synthesise cytokines or chemokines,^{14,39} some of which are already stored in pre-synthesised, rapidly mobilisable form in cytoplasmic secondary and tertiary granules.^{40,41} These include: (1) the pro-angiogenic growth factor vascular endothelial growth factor (VEGF), (2) the chemokine interleukin (IL)-8 and the cytokines IL-1 β , IL-6 and TNF, all of which interact to promote neutrophil extravasation, accumulation and activation and (3) IL-12 which links innate and adaptive immunity, promoting cell-mediated immune responses involving T helper 1 lymphocytes.^{14,39-41} With respect to tumour promotion/progression, the most prominent of these are VEGF, which promotes tumour neovascularisation, and IL-8, which not only sustains neutrophil influx and activation, but also promotes tumour cell proliferation by the autocrine and paracrine mechanisms described under 'Chemokines and tumourigenesis'.

Although the evidence is somewhat less compelling than that for VEGF and IL-8, several other neutrophil-derived cytokines have been implicated in tumour promotion/progression and angiogenesis. Because these have been extensively reviewed recently,¹⁴ they are considered only briefly here.

APRIL (also known as 'a proliferation-inducing ligand') and BAFF (B cell activation factor, BlyS), both of which belong to the TNF ligand family, interact with several receptors, especially BMCA (B cell maturation antigen), TAC1 and BAFF receptor, inducing B cell proliferation and survival. Both of these cytokines are produced by tumour-infiltrating neutrophils, and have been implicated in tumour promotion in malignancies such as diffuse large B cell lymphoma and multiple myeloma.¹⁴

Oncostatin M (OSM) and hepatocyte growth factor (HGF) are cytokines which are both stored and synthesised by tumour-infiltrating neutrophils. OSM appears to mediate tumour progression via induction of detachment of tumour cells and activation of synthesis of pro-angiogenic VEGF and fibroblast growth factor by endothelial cells, while HGF induces an invasive phenotype.¹⁴

These various cytokines and their reported roles in tumourigenesis are summarised in Table 3, with the exception of IL-8 which is discussed in detail below.

Table 3: Neutrophil-derived cytokines implicated in tumourigenesis

Cytokine	Pro-tumourigenic action
*Vascular endothelial growth factor (VEGF)	Tumour neovascularisation; pro-metastatic
*APRIL ('a proliferation-inducing ligand')	Tumour promotion; implicated in the aetiologies of diffuse large B cell lymphoma and multiple myeloma
*B cell activation factor (BAFF)	Tumour promotion; also implicated in the aetiology of B cell malignancies
*Oncostatin M (OSM)	Tumour progression
*Hepatocyte growth factor (HGF)	Tumour progression

*Recently reviewed by Tecchio et al.¹⁴

Chemokines and tumourigenesis

Chemokines are a group of low molecular weight chemotactic cytokines which promote the receptor-mediated migration of cells of the innate and adaptive immune systems. In the case of neutrophils, these cells are attracted to sites of tissue injury or infection by members of the sub-family of CXC/ELR-motif-positive chemokines (CXC denotes the presence of an intervening amino acid, X, between the first two conserved cysteine residues, while the ELR motif is a glu-leu-arg sequence preceding the first conserved cysteine residue). The various members of this chemokine sub-family are shown in Table 4, with the potent neutrophil chemoattractant IL-8 (CXCL8) predominating.

Table 4: Examples of neutrophil-targeted CXC/ELR⁺ chemokines

Systematic name	Alternative name
CXCL1	Growth-related oncogene (GRO)- α
CXCL2	Growth-related oncogene (GRO)- β
CXCL3	Growth-related oncogene (GRO)- γ
CXCL5	Epithelial neutrophil-activating peptide-78 (ENA-78)
CXCL6	Granulocyte chemotactic protein-2 (GCP-2)
CXCL7	Neutrophil-activating peptide-2 (NAP-2)
CXCL8	Interleukin-8 (IL-8)

Notwithstanding production by cells of the innate and adaptive immune systems, CXC/ELR⁺ chemokines, especially IL-8, are also produced by various types of structural cells, including epithelial and endothelial cells, fibroblasts and smooth muscle cells. The major counter-receptor for these CXC/ELR⁺ chemokines is CXCR2 (IL-8 also interacts with CXCR1), which is expressed not only on neutrophils and mast cells, but also on epithelial and endothelial cells.¹²

Importantly, and aside from their primary role in neutrophil mobilisation, CXC/ELR⁺ chemokines and CXCR2 are also expressed by a diverse range of human cancers, including cancers of the breast, bladder, cervix, colon, liver, lymphatics, oesophagus, ovary, prostate and skin.^{12,13,42} In this setting, these chemokines drive tumour expansion via both autocrine and paracrine pro-proliferative interactions with CXCR2-expressing tumour cells.^{12,13,42,43} In the case of oesophageal squamous epithelial cells, and probably other tumour cell types, CXCR2-mediated proliferation results from activation of the transcription factor early growth response-1.¹¹ In addition, tumour neovascularisation is mediated via the pro-angiogenic activities of these chemokines, especially IL-8,¹² while the chronic influx of inflammatory cells exacerbates ROS-mediated oxidative damage to DNA and immunosuppression.

Neutrophil-derived proteases in tumour angiogenesis and metastasis

Neutrophil-derived proteases – specifically elastase and matrix metalloproteinase-9 (MMP-9) stored in primary and secondary/tertiary granules, respectively – have also been implicated in inflammation-associated tumour neovascularisation and invasion. Elastase has been reported to degrade the intercellular adhesion molecule cadherin,⁴⁴ while MMP-9 is a potent inducer of angiogenesis and tumour metastasis.^{16,17}

Neutrophil adhesion molecules in tumour metastasis

Notwithstanding the expression of counter-receptors for endothelial adhesion molecules by some types of tumours,² pro-adhesive interactions between circulating neutrophils, albeit in an animal model

of experimental liver metastasis, have also been reported to mediate delivery of tumour cells to distant sites.⁴⁵ In this setting, neutrophil/tumour cell adhesion is mediated via interactions of the β 2-integrin Mac-1 on neutrophils, with its counter-receptor, intercellular adhesion molecule-1 (ICAM-1), on tumour cells.⁴⁵

The aforementioned mechanisms of neutrophil/inflammation-mediated tumourigenesis are summarised in Figures 1 and 2.

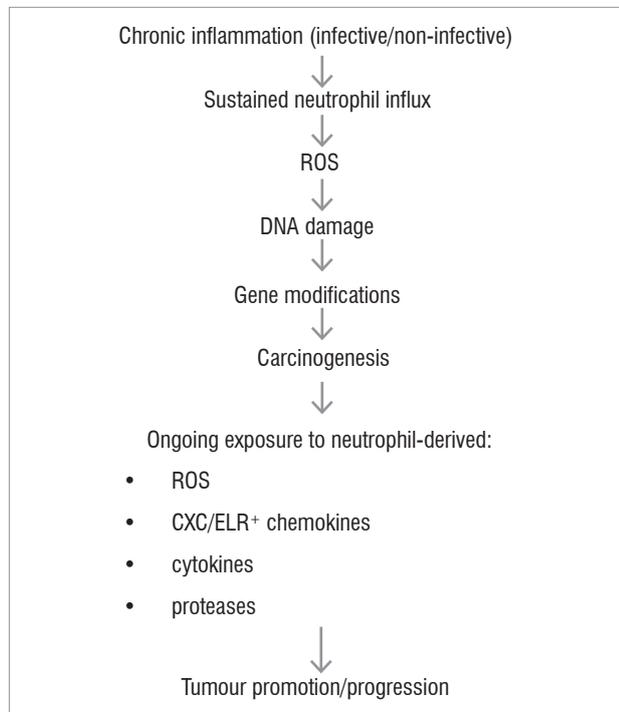


Figure 1: Proposed mechanism by which chronic inflammation leads to oxidative damage to the DNA of bystander tissue cells as a result of the sustained release of reactive oxygen species (ROS) from infiltrating neutrophils. Tumour initiation is followed by promotion and progression as a result of ongoing exposure to neutrophil-derived pro-proliferative and pro-angiogenic mediators.

Inflammation-targeted chemotherapy and immunotherapy in cancer

The chemopreventive potential of aspirin in particular, and possibly other non-steroidal anti-inflammatory drugs (NSAIDs), in reducing the incidence of colorectal cancer, and possibly other cancers, such as those of the liver, lung, oesophagus and stomach, is well recognised.^{2,19,46-48} Although the underlying mechanism is presumed to be anti-inflammatory in origin, other mechanisms, such as attenuation of prostaglandin E2-mediated inhibition of tumour-targeted T lymphocytes, have also been proposed.² In the case of therapy, the potential of NSAIDs as adjuncts to conventional anti-cancer therapies remains largely unknown, a possible exception being the use of aspirin in the treatment of colorectal cancer associated with *PIK3CA* gene mutations.^{49,50}

Other potential pharmacological strategies include the use of inhibitors of MMP-9, although these have proved disappointing in phase II/III clinical trials in various types of malignancy,⁵¹ and, perhaps the most promising strategy albeit unproven in the clinical setting, the use of pharmacological antagonists of CXCR2⁴³ and possibly dual antagonists of CXCR1/CXCR2. In addition to these, other categories of pharmacological agent which target the pro-inflammatory activities of neutrophils include 14/15-membered macrolide antibiotics and inhibitors of type 4 phosphodiesterase (PDE), the predominant PDE in human neutrophils. Unlike corticosteroids, which have limited efficacy in controlling neutrophilic inflammation, macrolides and PDE4 inhibitors possess a range of neutrophil-targeted anti-inflammatory activities

which have recently been described in detail elsewhere.⁵² Although untested with respect to their adjunctive potential as anti-inflammatory agents in cancer chemotherapy, it is noteworthy that novel macrolides and PDE4 inhibitors are currently under investigation for their direct anti-tumour activities.^{53,54}

Monoclonal antibody-based anti-inflammatory therapies include those which target VEGF in various types of metastatic cancer, a strategy which has enjoyed variable success.⁵⁵⁻⁵⁷ Although monoclonal antibodies which target neutrophil-mobilising cytokines such as TNF, IL-8 and, more recently, IL-17A^{58,59} have been proposed as adjunctive anti-inflammatory strategies in the therapy of cancer, inhibitors of CXCR2 appear to be a superior option.

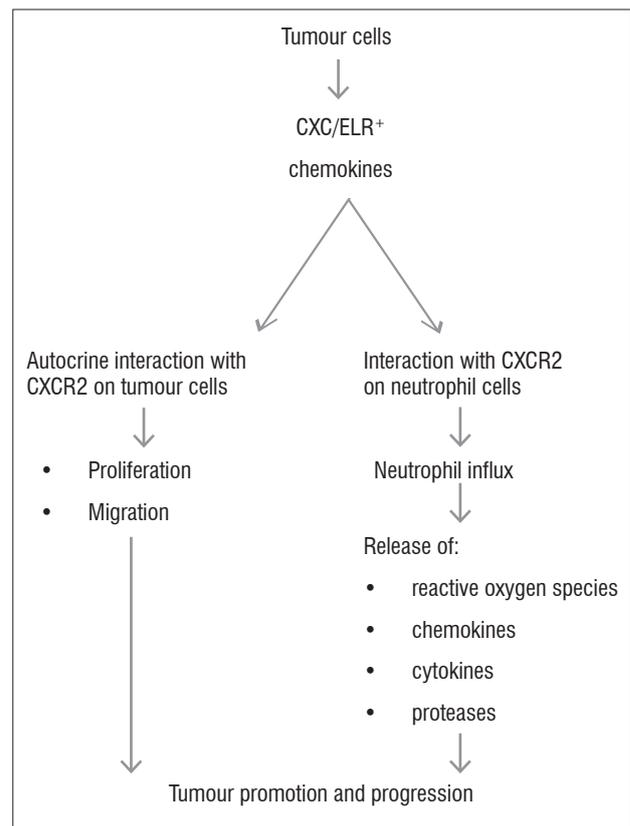


Figure 2: Proposed mechanism by which tumour-derived CXC/ELR⁺ chemokines exacerbate promotion and progression via the autocrine induction of proliferation and metastasis, as well as by recruitment of pro-tumourigenic neutrophils.

Conclusions

Although they are key players in innate host defence, human neutrophils are also inadvertent participants in the aetiology of inflammation-related cancers via the release of carcinogenic ROS and other mediators which contribute to tumour promotion and progression. Other types of cancer, which are not inflammatory in origin, also utilise inflammatory mechanisms to enhance their proliferative and invasive potential. The most significant of these mechanisms is the production of CXC/ELR⁺ chemokines. These chemokines not only recruit pro-tumourigenic neutrophils, but are also pro-proliferative and pro-metastatic via their autocrine interactions with CXCR2 expressed on tumour cells. These important insights into inflammation-associated mechanisms of tumourigenesis have enabled identification of potential anti-inflammatory adjunctive strategies to complement conventional anti-cancer therapies. However, given the range of neutrophil- and tumour-derived inflammatory mediators which contribute to tumourigenesis, selective targeting of a single mediator is unlikely to be successful. Although unproven in the clinical setting, selective antagonists of CXCR2, which target both neutrophils and tumour cells, represent a possible exception, as do NSAIDs, particularly aspirin. Preventive strategies include routine

intake of low-dose NSAIDs, immunisation against cancer-causing viral pathogens, early aggressive antimicrobial chemotherapy to eradicate chronic inflammation caused by microbial pathogens, and avoidance of pro-inflammatory aspects of lifestyle such as cigarette smoking and excessive exposure to ultraviolet radiation.

Authors' contributions

All authors were involved in the overall conception, planning, design and writing of the manuscript.

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