Oral Oncology 49 (2013) 887–892

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Inflammation in the context of oral cancer

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ARTICLE INFO

Article history:
Received 22 May 2013
Received in revised form 4 July 2013
Accepted 6 July 2013
Available online 30 July 2013

Keywords:
Oral squamous cell carcinoma
Cancer-associated inflammation
COX-2
STAT-3
AP-1
NF-κB
Oral submucous fibrosis
Oral lichen planus

SUMMARY

The link between cancer and inflammation is specific transcription factors that once activated have the capacity to enhance expression of genes that are common to both the regulation and the production of mediators of inflammation, and also to the regulation of the survival and proliferation of cancer cells. Cellular pathways activated by chronic inflammation brought about by chronic infections, by immune-mediated diseases, or by dysregulated wound healing at sites of repetitive tissue injury, constitute risk factors for initial cell transformation and for cancer progression. In established cancers, the cancer cells induce development of an exaggerated inflammatory state in the stroma, which in turn promotes cancer growth, invasion and metastasis. Inflammatory cells of myeloid origin in the tumour-associated stroma, mediate suppression of immune responses against cancer cells, which suppression favours tumour growth.

Oral submucous fibrosis, and to a lesser extent oral lichen planus are precancerous conditions in which immuno-inflammatory processes are implicated in their pathogenesis, and in their cancerous transformation, if it occurs. Although there is some evidence for an association between oral squamous cell carcinoma on the one hand and dento-gingival bacterial plaques and chronic periodontitis on the other hand, the role of inflammation as the sole cause of cancerous transformation in such cases is not proven.

The purpose of this article is to elaborate on some of the more important relationships between oral cancer and inflammation, and to comment on the role of inflammation in the pathogenesis of oral squamous cell carcinoma.

Introduction

There is evidence that chronic inflammation brought about by persistent chemical, bacterial or viral agents is a risk factor for cancer [1–7]. For example, chronic infection with *Helicobacter pylori* is associated with gastric cancer, chronic viral hepatitis B or C is associated with hepatocellular cancer, and chronic pancreatitis or chronic prostatitis of non-specific origin are associated with cancers of the pancreas or of the prostate, respectively [3,5,6]. Dysregulated inflammatory processes brought about by certain autoimmune reactions, or by minor, persistent repetitive soft tissue trauma, also impose a risk of cancer [8].

Cytokines, chemokines, prostaglandins and reactive oxygen and nitrogen radicals accumulate in the microenvironment of tissues affected by chronic inflammation. If persistent, these inflammatory factors have the capacity to induce cell proliferation and to promote prolonged cell survival through activation of oncogenes and inactivation of tumour-suppressor genes. This may result in genetic instability with an increased risk of cancer [3,9].

In genetically altered cells at different stages of transformation, the intrinsic cellular circuits that bring about increased cell proliferation and cell survival may also bring about the production and secretion of inflammatory mediators. These biological mediators generate an inflammatory microenvironment that further increase cell survival and proliferation of the transformed cells, as well as promoting angiogenesis and evasion of protective immune responses [3,5,6]. Once an inflammatory microenvironment has been established, reciprocal interactions between the evolving tumour cells and their stromal cells sustain cancer cell proliferation and promote the progression of the tumour [4,10]. Thus, common transcription factors that normally regulate genes producing inflammatory mediators, and genes controlling cell survival and proliferation are the link between cancer and inflammation [9].

However, as chronic inflammatory processes of the oral mucosa are common and as cancers of the oral mucosa are relatively uncommon, it is evident that inflammatory processes on their own only rarely induce cancer development [6,11].

The aim of this short review is to outline the association between inflammation and cancer and to shed light on the role of inflammation in the pathogenesis of oral squamous cell carcinoma.

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http://dx.doi.org/10.1016/j.oraloncology.2013.07.003

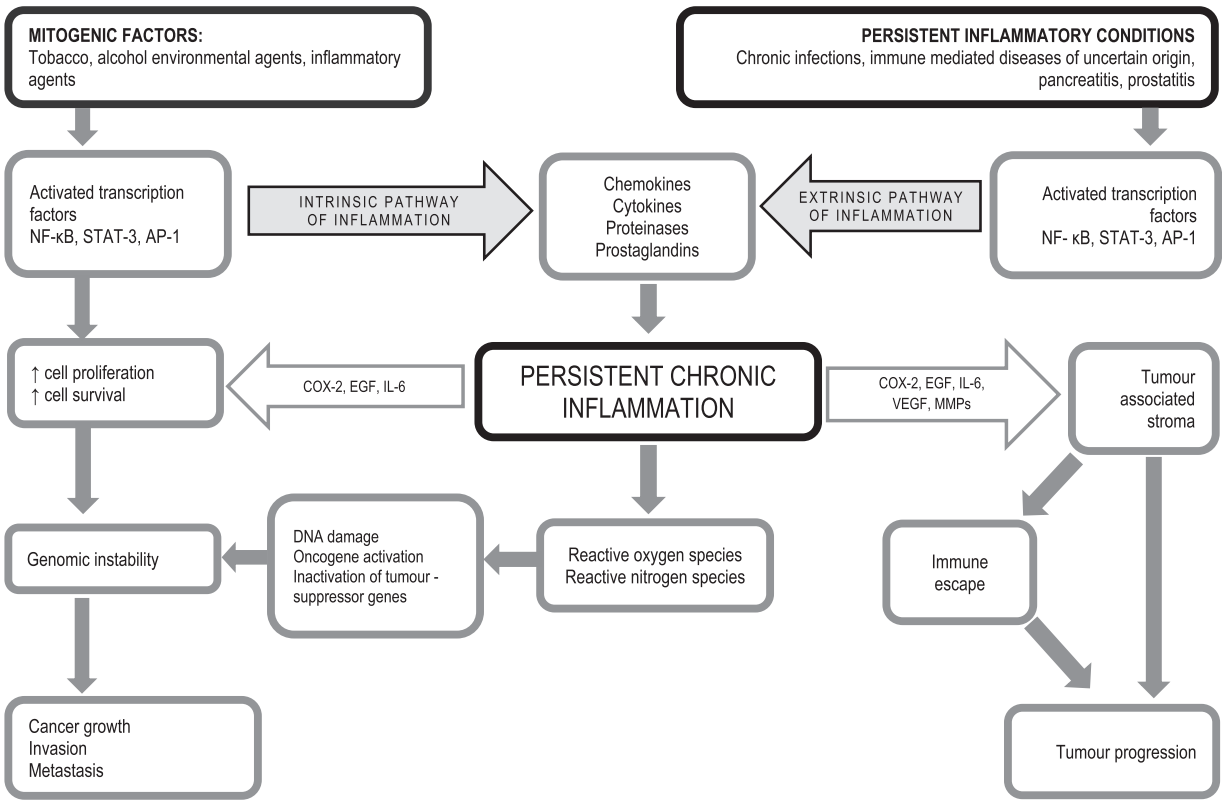

Figure. 1. The interaction between cancer and inflammation. In the intrinsic pathway, activated transcription factors that regulate both oncogenic circuits and inflammation related programs, drive the process of tumour development. In the extrinsic pathway, pre-existing inflammatory conditions may favour the onset of cancer and promote tumour progression (adapted from Mantovani, 2010).

Inflammation-driven carcinogenesis and cancer-induced inflammation

Tobacco, alcohol, certain environmental and infectious agents and inflammatory mediators have the capacity to activate the nuclear signal transducers and activators of transcription-3 (STAT-3), the activator protein-1 (AP-1) and the nuclear factor-$_k$B (NF-$_k$B). In turn, these transcription factors activate oncogenes regulating apoptosis, cell proliferation and angiogenesis; and genes regulating the production of inflammatory mediators including growth factors, cytokines, prostaglandins and proteinases [1–3,5,12]. Thus, through these common transcription factors, cancer cells, concurrently induce both inflammation and uncontrolled self-proliferation (intrinsic pathway) (Fig. 1). The inflammatory microenvironment in turn, is conducive to tumour progression. This intrinsic pathway explains why inflammatory cells and inflammatory mediators are almost invariably present in the microenvironment of all cancer types [3,5].

In addition, there is cross talk between cancer cells and non-cancer cells within the tumour-associated stroma. The cancer cells induce the secretion of inflammatory mediators by immuno-inflammatory cells within the stroma; the inflammatory mediators in turn induce cancer cell proliferation and survival, and the angiogenesis essential to tumour progression [4]. This might explain why cancers that are rapidly progressing, microscopically show an intense inflammatory infiltrate [8].

In inflamed non-cancerous tissues the transcription factors mentioned above may bring about an increase in cell proliferation and prolonged cell survival that may favour initial cancerous transformation (extrinsic pathway) (Fig. 1) [2,3,5]. Inflammatory cells may secrete reactive oxygen species and reactive nitrogen species that have the capacity to cause direct DNA damage, and to dysregulate mechanisms of DNA repair, of cell-cycle checkpoint control and of apoptosis. This brings about a genomic instability favouring the evolution of random mutations and development of cancer [3,4,8]. Reactive nitrogen species may also act as mediators of intracellular signalling circuits including the mitogen-activated protein kinase (MAPK) signallingpathway that plays a part in inducing cell proliferation and differentiation [1]. Thus, inflammatory pathways activated by the chronic inflammation of chronic infections, autoimmune diseases, or by repetitive and habit-related chemical trauma may not only promote cancer progression but may also constitute the risk factors of initial cell transformation [7,8,10].

Molecular patterns of microorganisms associated with pathogenesis, specific moieties which are the by-product of tissue damage, and inflammatory cytokines including TNF-α and IL-1β, have the capacity to trigger Toll-like receptor (TLR)-MyD88 intracellular signalling pathways in epithelial cells and in immuno-inflammatory cells of the innate arm of the immune system. These activated signalling pathways mediate the production of inflammatory factors that in turn activate NF-κB, STAT-3 and AP-1 transcription factors. These promote cell survival by upregulating expression of anti-apoptotic genes and of genes regulating cell cycle checkpoints, including c-Myc, Mc-1, cyclin-D, Bcl-2, c-Flip and survivin, thus bringing about a state of cellular genomic instability [3,5,12].

Out of all the proinflammatory members of the prostaglandin (PG) family, PGE-2 is the one most frequently implicated in cancerization [13]. While cyclo-oxygenase-1 (COX-1) is expressed constitutively in most tissues producing prostaglandins that mediate physiological activities, COX-2 is expressed mainly in response to inflammatory and mitogenic stimuli [13–15]. COX-2 is an important enzyme in PGE-2 biosynthesis [13,16]; it is expressed at high levels in different types of epithelial malignancies and its expression is