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The role of IL-6 and STAT3 in inflammation and cancer

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Abstract

The defense of the host from foreign pathogens is the commonly accepted function of the vertebrate immune system. A complex system consisting of many differing cells and structures communicating by both soluble and cell bound ligands, serves to protect the host from infection, and plays a role in preventing the development of certain types of tumours. Numerous signalling pathways are involved in the coordination of the immune system, serving both to activate and attenuate its responses to attack. The ability of the immune system, specifically those cells involved in acute inflammatory responses, to mediate the directed (and sometimes indirect) killing of cells and pathogens, make it a potential threat to host survival. Furthermore, the production and release of various survival factors such as the pleiotropic cytokine IL-6, a major mediator of inflammation and activator of signal transducer and activator of transcription 3, serves to block apoptosis in cells during the inflammatory process, keeping them alive in very toxic environments. Unfortunately, these same pathways serve also to maintain cells progressing towards neoplastic growth, protecting them from cellular apoptotic deletion and chemotherapeutic drugs. Here, we discuss the relationships between cancer and inflammation, and some of the molecular mechanisms involved in mediating the unintended consequences of host defense and tumour survival.

Keywords: Inflammation; STATs; IL-6; Cancer; JAK; Kinase inhibitor; Resistance to chemotherapy

1. Introduction

Cornelius Celsus, a physician in first century Rome, first described the four primary signs of inflammation as heat (*calor*) pain, (*dolor*), redness (*rubor*), and swelling (*tumour*). The use of the Latin derivation "tumour" to describe swelling seems prescient given recent discoveries and developments in oncology. Inflammation follows infection, and is most commonly observed as a part of the defense mechanisms triggered to protect the host from pathogens. However, recent evidence suggests that the immune system more closely resembles a "double edged sword," rather than a benign protector [1]. Tissue damage can also be followed by inflammation, a necessary step to remove necrotic debris. In order to destroy the incoming pathogens, a myriad of cellular and molecular factors are unleashed against the invader, producing an attack that occurs on multiple levels [2–4]. The recruitment of macrophages into the area of the infection represents a major phase of the inflammatory response [5]. The production of reactive oxygen species (ROS) by macrophages, along with highly efficient proteases, degrade the pathogens down to mere fragments of peptides, that are then presented to lymphocytes involved in the second phase of the response [6].

This entire process is controlled by the synthesis and release of various peptide mediators of the immune response, consisting primarily of cytokines and chemokines [7,8]. Typically, cytokines, also known as interleukins, function through the binding and subsequent stimulation of cellular receptors that are associated with

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a family of tyrosine kinases known as Janus kinases (JAK) [9]. Chemokines on the other hand, function by binding to heptahelical receptors, triggering the activation of heterotrimeric GTP-binding proteins [10]. Also involved in this process are prostaglandins and leukotrienes [11], lipid second messengers that reinforce the inflammatory response [12]. The overlapping functions of these pathways are numerous, and redundant, for without such a system death would be inevitable in our microbe infested world. However, despite the lethality of the immune system, the host survives due to the protective effects of various inflammatory mediators [13,14]. Indeed, cells of the immune system, and those they are protecting, would certainly perish in the very toxic environment of the inflammatory response were it not for the protective effects of cytokines and chemokines. For example, it has been reported that one of the most common inflammatory cytokines, Interleukin-6 (IL-6), is known to mediate many unwanted, detrimental effects such as resistance to chemotherapeutic drugs [15,16]. It now seems apparent that in addition to driving inflammatory mechanisms, cytokines such as IL-6 have the ability to protect cells from the "byproducts" of inflammation (such as ROS and free-radical damage), and that this protective effect extends also to cells that might have strayed somewhat from normal cell cycle regulatory pathways [17]. A possible scenario depicting the series of events leading to neoplastic growth is shown in Fig. 1.

2. IL-6: a ruthless cytokine

Interleukin (IL)-6 is a potent, pleiotropic, inflammatory cytokine that mediates a plethora of physiological functions, including the developmental differentiation of lymphocytes, cell proliferation, and cell survival and amelioration of apoptotic signals [18–20]. Additionally, IL-6 exerts effects on bone formation, general system metabolism, endocrine functions, and can affect many cells of other tissues and organ systems [21,22]. Depending upon the cell type, IL-6 is able to act through several classic protein kinase cascades such as mitogen activated protein kinase (MAPK), and phosphatidylinositol-triphosphate kinase (PI-3 kinase) (Fig. 2) [23]. The ability of IL-6 to directly activate the signal transducers and activators of transcription (STAT) factors STAT1 and STAT3, via the JAK produces serious unintended

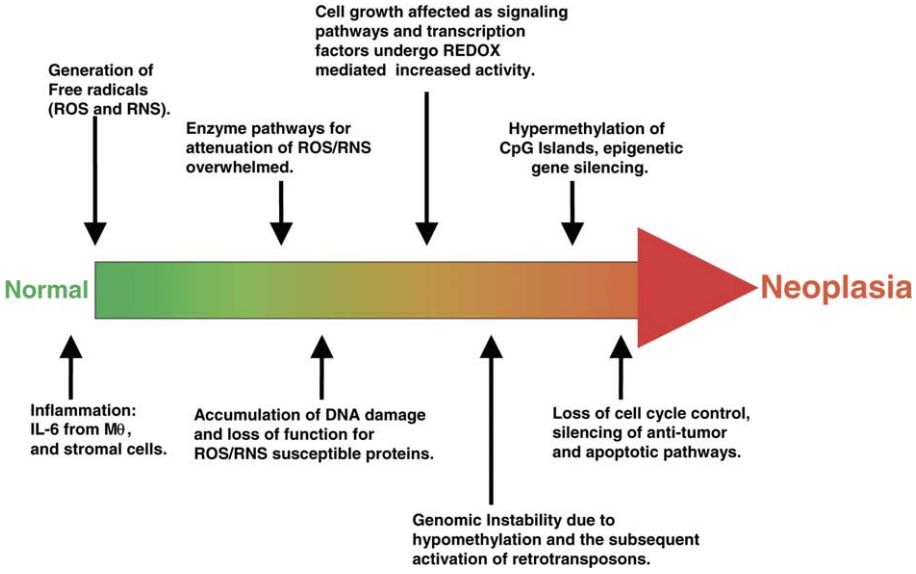

Fig. 1. *Proposed model for progression to neoplastic growth starting from the dysregulation of the inflammatory response.* Following stimulation of the cells (macrophages, neutrophils, stromal, and others) to mediate an inflammatory response, cytokines such as IL-6 are released and activate the requisite signaling pathways involved in host defense. The generation of free radicals, including reactive oxygen and nitrogen species (ROS and RNS, respectively), begins accompanied by changes in REDOX conditions. While having specific purposes, these highly reactive compounds are capable of covalently modifying proteins, nucleic acids, and lipids. Enzyme pathways that function to attenuate the excess free-radicals, *i.e.* superoxide dismutases (MnSOD, Cu/ZnSOD), DNA repair enzyme systems, protein de-nitrosylation, have a limited input capacity and are probably overwhelmed when inflammation is chronic in nature. Simply stated, the repair of DNA damage is really a function of enzyme rates, if the repairs can be affected in the time available between cell cycles point mutations will not be passed on to daughter cells. However, in the event of repeated and constant inflammation, the cytokine signals prevent apoptosis even in the face of DNA damage hence some point mutations are retained. Furthermore, since increases in oxidative free radicals have been shown to drive proliferation by activating various kinases, increased ROS/RNS levels would tend to favor proliferation, decreasing the time available to repair mutations. It is possible that enzymes involved in methylation may be targets of inflammatory dysregulation, as genomic hypomethylation and promoter hypermethylation are commonly observed in many tumour types. These multiple insults eventually lead to unregulated proliferation, and hypoxic conditions that accompany such growth are thought to trigger vascularisation of solid tumours and metastasis.