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PII: S1044-579X(17)30210-9
DOI: http://dx.doi.org/10.1016/j.semcancer.2017.08.006
Reference: YSCBI 1371

To appear in: *Seminars in Cancer Biology*

Received date: 6-9-2016
Revised date: 8-8-2017
Accepted date: 9-8-2017

Please cite this article as: Qian Bin-Zhi.Inflammation fires up cancer metastasis.*Seminars in Cancer Biology* http://dx.doi.org/10.1016/j.semcancer.2017.08.006

Inflammation fires up cancer metastasis

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Abstract: Metastatic disease is the major challenge of cancer that accounts for over 90% of total cancer lethality. Mounting clinical and preclinical data now indicate that inflammation, a potent immune and repair response, is indispensable for metastasis. In this review we describe our current understanding of how major inflammatory cells contribute to metastatic cascade with a focus on the primary tumour. We also discuss exciting new directions for future research and novel therapeutic approaches to tackle metastatic disease through targeting inflammation.

Keywords: metastasis; inflammation; cancer; immunology

Introduction

Inflammation is a response that an organism uses to resolve infection, tissue injury or other cellular stress, and to restore tissue function through repair mechanisms [1]. It is a sophisticated process involving extensive crosstalk among different immune cells as well as non-immune cells, such as epithelial cells, endothelial cells and fibroblasts. Unlike normal tissue, cancer involves continuous cell renewal and proliferation that induces persistent inflammation [2]. In fact, inflammation is observed in almost every cancer and is one of the hallmarks of cancer [3]. Cancer associated inflammation involves crosstalk between both malignant and nonmalignant cells through mediators (e.g. cytokines, chemokines and prostaglandins) in autocrine and paracrine manner [4]. Joint forces with genetic alteration, the inflammatory tumour environment eventually leads to tumor progression and metastasis [5]. For example, inflammatory response associated with epithelial cell senescence contributes significantly to transformation and carcinogenesis in the absence of p53 tumour suppressor gene, which can be inhibited with anti-inflammatory drugs [6]. Treatment with the anti-inflammatory drug dexamethasone also significantly suppressed cancer dissemination through suppression of epithelial to mesenchymal transition (EMT), a process epithelial cell uses to obtain migratory and invasive properties [7]. Thus, inflammation is an indispensable driver for cancer metastasis.

Mechanistically, tumour associated inflammation produces mutagenic factors (e.g. reactive oxygen species) that drive tumour initiation[5]. Tumour associated inflammation is a source of survival, growth and pro-angiogenic factors, as well as extracellular matrix (ECM)-modifying enzymes that facilitate angiogenesis, invasion and metastasis [8, 9]. Inflammation induced angiogenesis not only provides necessary nutrients for tumour growth, but also provides a ‘highway’ for tumour to escape from the