Macrophages in tumour development and metastasis

Alexandra Eichten¹², Karin E. de Visser¹³, and Lisa M. Coussens²⁴⁵⁶

Abstract: Activated stromal cells, e.g. inflammatory cells, fibroblasts and vascular cells, present in tumour microenvironments profoundly influence neoplastic development and progression to the tumour state. Macrophages are multifunctional immune cells that often constitute a major component of the inflammatory cell repertoire associated with premalignant and malignant tissues. Macrophages are recruited from the blood circulation by tumour-derived chemoattractants and preferentially localize to hypoxic tumour regions. Depending on their activation status and microenvironment, macrophages can impact tumour development and progression by either positive or negative mechanisms. Based upon this duality, the macrophage balance theory was proposed to emphasize complex relationships between tumour-associated macrophages and neoplastic cells. When appropriately activated, as during acute inflammatory responses, macrophages manifest an M1 phenotype and gain tumouricidal capacities; however, under adverse conditions present within tumour microenvironments, macrophages adopt an M2 phenotype and functionally contribute to neoplastic progression and overall tumour development.

Keywords: Angiogenesis, Cancer, Inflammation, Macrophage, Metastasis

Introduction

Macrophages are the major terminally differentiated cells of the mononuclear phagocyte system (Janeway et al. 2001). They are released from bone marrow as immature monocytes and circulate in the bloodstream before entering tissues (Gordon 2003). After extravasation from the blood vasculature, monocytes undergo final differentiation into resident organ specific macrophages (Mantovani et al. 2007) such as alveolar macrophages in lung, Kupffer cells in liver and osteoclasts in bones. Macrophage literally means “big eater”. Initially, macrophages were described as cells specialized in uptake and digestion of foreign intruders and removal of dead cells; however, our knowledge of the vast repertoire of functions they regulate has expanded significantly.

Macrophages are versatile cells with capability to adapt their metabolism, phenotype and functional capacities to their microenvironment. As a consequence...
of this flexibility, macrophages survive and function under adverse circumstances, including healing wounds and hypoxic areas within tumours (Lewis et al. 1999; Crowther et al. 2001). Macrophages require activation in order to exhibit their cytotoxic activity (Gordon 2003; Mantovani et al. 2002). Appropriately activated macrophages can exert direct cytotoxic effects on “abnormal” cells, phagocytose and process foreign material, debris and dead cells, and present antigens to lymphocytes, thus linking the innate with the adaptive immune system (Gordon 2003; Mantovani et al. 2002). In addition, macrophages produce various factors, including pro- and/or anti-inflammatory cytokines, chemokines, proteases, reactive oxygen species (ROS) and growth factors (Gordon 2003; Mantovani et al. 2002) thereby influencing a wide array of cells and processes in their local microenvironment; thus, macrophages are considered crucial players in diverse physiological and pathological processes including wound healing (Crowther et al. 2001), asthma (Poulter et al. 1994) and cancer (Mantovani 1994; Mantovani et al. 1992).

Cancer is a progressive disease typically requiring initial mutations in proliferating cells that are necessary but not sufficient for progression to the tumour state (Hanahan and Weinberg 2000). Additional genetic and epigenetic changes render initiated cells self-sufficient for growth, insensitive to growth-inhibitory signals and resistant to programs of terminal differentiation, senescence or apoptosis (Hanahan and Weinberg 2000) that together support unlimited self-renewal, activation of angiogenic and tissue remodeling programs and the ability to survive and invade into ectopic tissue environments (Hanahan and Weinberg 2000; Bissell and Radisky 2001). While tumours are composed of neoplastic cells, they also contain a diverse array of activated stromal cells, including endothelial cells forming the blood vasculature and lymphatics, fibroblasts and immune cells, all of which co-exist in a dynamic extracellular matrix (ECM) that together foster cancer development. Macrophages compose a large percentage of the total immune cell repertoire in many tumour types (Coussens and Werb 2001; Balkwill and Mantovani 2001; Ishigami et al. 2003; Noguchi et al. 2003; Li et al. 2002; Hamada et al. 2002; Funada et al. 2003; Lewis and Pollard 2006) and accumulating clinical data suggest that their presence influences tumour development by both pro- and anti-tumour mechanisms (Mantovani 1994; Mantovani et al. 1992; Bingle et al. 2002; Ohno et al. 2002). In human gastric cancer, the degree of macrophage infiltration positively correlates with worse clinical outcome (Ishigami et al. 2003). Likewise, clinical prognosis of patients with renal cell carcinoma containing high numbers of tumour-associated macrophages (TAMs) is poor (Hamada et al. 2002), and in patients with oral cancer, abundance of TAMs is associated with local invasion and increased vessel density (Li et al. 2002). In contrast, other studies have described a beneficial effect of macrophage infiltration in human cancer. The overall survival rate of patients with colorectal cancer containing high numbers of tumour-infiltrating macrophages and CD8+ T cells is higher than those with low numbers of macrophages and CD8+ T cells (Funada et al. 2003). In addition, the number of intratumoural CD68+ macrophages is significantly greater in esophageal carcinoma patients without lymph node metastasis (Noguchi et al. 2003). The exact cellular and/or molecular mechanisms underlying these contradictory correlations between macrophage infiltration and tumour progression remain to be elucidated; however, it is likely that the dual role of macrophages during tumour development owes to their activation and differentiation status. In this chapter, we discuss the controversial relationship between tumours and macrophages, mechanisms by which macrophages are recruited towards neoplastic tissues and the influence of the tumour microenvironment on their differentiation and activation status, as well as how pro- and anti-tumour functions of macrophages either contribute to or retard neoplastic development.

Recruitment of macrophages to neoplastic lesions

Neoplastic cells and activated stromal cells present in tumour microenvironments secrete a diverse array of polypeptide growth factors, cytokines and chemokines that regulate recruitment of leukocytes (Mantovani 1994; Balkwill and Mantovani 2001; Baggioi and Loetscher 2000; Zlotnik and Yoshie 2000; Payne and Cornelius 2002; Silzle et al. 2003) (Table 1), the presence of which can differentially regulate either pro- or anti-tumourigenic programs. Accumulation of macrophages is a common phenomenon in many human