Immunobiology 222 (2017) 21–30

Contents lists available at ScienceDirect

Immunobiology

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

Review

The delicate balance of macrophages in colorectal cancer; their role in tumour development and therapeutic potential

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ARTICLE INFO

Article history:
Received 14 April 2015
Received in revised form 28 July 2015
Accepted 29 August 2015
Available online 1 September 2015

Keywords:
Macrophages
Colorectal cancer
Immune therapy
Macrophage activation
Monoclonal antibodies

ABSTRACT

Most tumours are heavily infiltrated by immune cells. This has been correlated with either a good or a bad patient prognosis, depending on the (sub) type of immune cells. Macrophages represent one of the most prominent leukocyte populations in the majority of tumours. Functions of macrophages range from cytotoxicity, to stimulation of tumour growth by secretion of cytokines, growth and angiogenic factors, or suppressing immune responses. In most tumours macrophages are described as cells with immune suppressing, and wound healing properties, which aids tumour development. Yet, increasing evidence shows that macrophages are potent inhibitors of tumour growth in colorectal cancer. Macrophages in this respect show high plasticity. The presence of high macrophage numbers in the tumour may therefore become advantageous, if cells can be reprogrammed from tumour promoting macrophages into potent effector cells. Enhancing cytotoxic properties of macrophages by microbial products, pro-inflammatory cytokines or monoclonal antibody therapy are promising possibilities, and are currently tested in clinical trials.

Contents

Abbreviation: ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCG, bacillus calmette-guérin; CDC, complement-dependent cytotoxicity; CSF-1, colony stimulating factor 1; CTL, cytotoxic T lymphocyte; EGFR, epithelial growth factor receptor; FcγR, IgG Fc receptor; GM-CSF, granulocytic-macrophage colony stimulating factor; HLA-DR, human leukocyte antigen DR; HRG, histidine-rich glycoprotein; IFN-γ, interferon-γ; IgG, immunoglobulin G; IL-12, interleukin 12; LPS, lipopolysaccharides; mAb, monoclonal antibody; MDSC, myeloid derived suppressor cell; MHCII, major histocompatibility complex class 2; MMP9, metalloproteinase 9; MTP-PE, muramyl-tripeptide phosphatidyl-ethanolamine; NK cell, natural killer cell; NO, nitric oxide; PyMT, polyoma middle T oncoprotein; ROS, reactive oxygen species; TAM, tumour associated macrophage; Th1, T-helper 1 cell; TLR, toll like receptor; TNFα, tumour necrosis factor-α; VEGF, vascular endothelial growth factor.

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http://dx.doi.org/10.1016/j.imbio.2015.08.011
0171-2985/

1. Introduction

Cancer development is a multistep process of sequential mutations in oncogenes and tumour suppressor genes of normal cells, resulting in the transformation into a tumour cell (Croce, 2008; Hanahan and Weinberg, 2011). Subsequent uncontrolled cell division typically progresses from pre-cancerous lesions into malignant tumours. However, in addition to alterations in tumour cells also the micro-environment is essential to drive progression of malignancies. As the tumour grows it needs increasing amounts of oxygen and nutrients and therefore interacts with surrounding tissues and vessels. For example, different stromal cell types such as fibroblasts and endothelial cells will infiltrate the growing tumour mass, leading to neoangiogenesis and vascularisation of the tumour (Allen and Louise, 2011; Papetti and Herman, 2002). Additionally, cells of the immune system play an important role in the initiation and development of cancer (Mariani et al., 2014). Immunosurveillance may on the one hand lead to killing of tumour cells, and on the other hand, chronic inflammation can result in exposure to harmful mediators such as reactive oxygen species, which predisposes for developing cancer (Coussens et al., 2013). Moreover, immune cells that have infiltrated a tumour mass can create a micro-environment in which cytokines, chemokines, growth factors, and angiogenic factors are produced that promote tumour progression (Allen and Louise, 2011; Chow et al., 2012).

Especially innate myeloid cells are frequently considered the culprits in immune (dys) regulation and tumour progression (Balkwill and Mantovani, 2012). These comprise of, amongst others, myeloid derived suppressor cells (MDSCs), which are immature myeloid cells that can be subdivided into monocytic and granulocytic MDSCs (Gabrilovich et al., 2012; Movahedi et al., 2008; Youn et al., 2008). Both types of MDSCs have been described to suppress cytotoxic T lymphocyte (CTL) or $CD8^+$ T cell function. Tumour-associated neutrophils (TAN) can also manipulate the tumour micro-environment, for instance by stimulating angiogenesis through secretion of matrix metalloproteinase 9 (MMP9) (Tazzyman et al., 2009). However, among the infiltrating myeloid immune cells, macrophages are particularly abundant and play plethora of functions in tumour development (Grivennikov et al., 2010; Hao et al., 2012).

Traditionally, macrophages have been described as tumouricidal cells. Increasing evidence, however, indicates that macrophages can adopt a pro-tumour phenotype in both primary tumours and metastases, as they can promote growth, angiogenesis, metastasis and immunosuppression (Biswas and Mantovani, 2010). Preclinical experimental models and clinical studies point to a pro-tumoural role of tumour-associated macrophages (TAMs) in many, if not most, types of malignancies. Colony stimulating factor-1 (CSF-1) is one of the most prominent growth and chemotactic factors for macrophages (Chitu and Stanley, 2006). In a mouse model for breast carcinoma caused by expression of the Polyoma Middle T oncoprotein (PyMT), absence of CSF-1 delayed development of adenomas into metastatic carcinomas. Moreover, transgenic CSF-1 expression in mammary epithelium accelerated late stage carcinoma development and pulmonary metastasis (Lin et al., 2001). This was likely due to local macrophage recruitment (Lin and Pollard, 2007; Wyckoff et al., 2007). Furthermore, extensive immune cell infiltration – which consisted primarily of macrophages –, in mamma carcinoma tumours was associated with augmented malignancy and enlarged tumour size (Lee et al., 1997). Similarly, an increased number of CD68-positive macrophages in tumours from patients with invasive breast carcinomas correlated with worse prognosis (Al Murri et al., 2007; Goede et al., 1999; Leek et al., 1996). The correlation between increased macrophage infiltration into the tumour and poor survival is currently not only evident for invasive breast carcinomas, but also for a variety of other human malignancies, including bladder carcinoma, cervix or endometrial tumours, melanoma, oesophagus carcinoma, renal cell carcinomas, cholangiocarcinoma and non-Hodgkin lymphoma (Farinha et al., 2005; Fujimoto et al., 2000; Hamada et al., 2002; Hanada et al., 2000; Hasita et al., 2010; Koide et al., 2004; Makitie et al., 2001; Ohno et al., 2004; Salvesen and Akslen, 1999; Steidl et al., 2010; Torisu et al., 2000; Vacca et al., 1999). In these malignancies it was demonstrated that patients with tumours containing high levels of infiltrated macrophages had worsened clinical stage of tumours, higher neovascularisation or vascular invasion, increased disease progression, more distant or lymph node metastases, or decreased 5-year (disease free) survival. The consensus of these studies was that the extent of macrophage infiltration into the tumour is a prognostic factor for poor prognosis.

The functions of TAMs in colorectal cancer are however not as straightforward. Macrophages have been implicated in inflammation-associated increased risk of developing colorectal cancer, such as in patients with inflammatory bowel disease (Erreni et al., 2011; Wang et al., 2015). Furthermore, a number of retrospective studies reported conflicting data on the correlation between macrophage presence and patient prognosis. Nonetheless, most studies support that, in contrast to other malignancies, increased macrophage infiltration is associated with better patient prognosis, (Forssell et al., 2007; Funada et al., 2003; Khorana et al., 2003; Lackner et al., 2004; Nagorsen et al., 2007; Shabo et al., 2014; Zhou et al., 2010). Thus, overall is the extent of macrophage infiltration into the tumour an independent prognostic factor for disease free-, relapse free- and overall survival.

In this review, we discuss the different roles of macrophages in colorectal cancer, and highlight several possibilities to influence macrophage behaviour as therapeutic strategies to treat cancer.

2. TAM in colorectal cancer

Colorectal cancer is one of the most prevalent cancers in both males and females. Worldwide approximately 1.36 million patients are diagnosed with this malignancy each year, and annually ~700.000 patients die because of this disease (International agency for research on cancer, 2015; Jemal et al., 2011). About 10 per cent of colorectal cancer cases develop as part of a well-defined hereditary syndrome. Additionally, an inflammatory micro-environment can contribute significantly to development of colorectal cancer, as patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) are predisposed to this malignancy (Erreni et al., 2011; Grivennikov, 2013; Gupta et al., 2007; Itzkowitz and Harpaz, 2004; Mariani et al., 2014). However, most colorectal cancers will arise sporadic due to (sequentially) acquired mutations.