Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Can the co-dependence of the immune system and angiogenesis facilitate pharmacological targeting of tumours?

Lorenzo Mortara[1], Andrew V Benest[2], David O Bates[2] and Douglas M Noonan[1,3]

Tumours elicit a number of mechanisms to induce a reprogramming of innate and adaptive immune cells to their advantage, inducing a pro-angiogenic phenotype. Investigation of these events is now leading to the identification of specific myeloid and lymphoid cell-targeted therapies, as well as of unexplored off-target activities of clinically relevant chemotherapeutic and metabolic drugs. It is also leading to an enhanced understanding of the interplay between angiogenesis and the immune system, and the value of novel co-targeting approaches using both immunotherapy and anti-angiogenic therapy. Here, we review recently identified mechanisms and potential pharmacological approaches targeting the crosstalk between cancer cells and the host immune system, providing an overview on novel therapeutic opportunities linking immuno-oncology and anti-angiogenic therapy.

Addresses
[1] Immunology and General Pathology Laboratory, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy
[2] Cancer Biology, Division of Cancer and Stem Cells, School of Medicine, University of Nottingham, Queen's Medical Centre, Nottingham NG2 7UH, UK
[3] Scientific and Technology Pole, IRCCS MultiMedica, Milan, Italy

Corresponding author: Noonan, Douglas M (douglas.noonan@uninsubria.it)

Current Opinion in Pharmacology 2017, **35**:66–74

This review comes from a themed issue on **Cancer**

Edited by **Antonio Sica**

http://dx.doi.org/10.1016/j.coph.2017.05.009

Introduction

In clinically relevant solid cancers, most of the tumour mass are host cells compared to transformed cells. The tumour tissue contains cells of the immune system, including myeloid-derived cells (macrophages, neutrophils, dendritic and myeloid-derived suppressor (MDSC) cells) and lymphoid-derived cells ($CD4^+$ and $CD8^+$ T cells, T regulatory (Treg) and innate lymphoid (ILCs) cells). These cells have the capacity to eliminate tumour cells, however, they are polarized toward a pro-tumour, pro-angiogenic phenotype that releases growth factors into the tumour microenvironment, stimulating angiogenesis, repressing adaptive and innate immune responses, and facilitating tumour growth [1,2].

The 'angiogenic switch' represents a critical point for tumour progression and is one of the hallmarks of cancer [3] that provides a base for the lymph node and distant metastases. Several 'anti-angiogenic' drugs are currently used in the clinic and more are being developed. The problem with most of these drugs is that they target a single angiogenic pathway, such that resistance develops due to the myriad of pathways that can lead to vessel development. Immune cells can also produce angiogenic factors that enable the tumour to escape anti-angiogenic drugs [4].

Here, we review the recent data in the literature focusing on the impact of modified immune cell functions related to the tumour angiogenesis cascade and how this point is becoming a valid target for innovative anti-cancer therapies and prevention.

Pro-tumour angiogenic innate immune myeloid-derived cells

Tumour-associated macrophages (TAMs) represent an important component of the tumour tissue with altered functions depending on the tumour type. The majority of macrophages present in the growing tumour have an 'M2' polarized phenotype [5,6] and are associated with tissue remodelling, growth promotion, and angiogenesis. It has been shown that for several tumours, TAMs correlate with a poor clinical prognosis and a favourable microenvironment for tumour invasion and angiogenesis [5–7]. The activation and polarization state of macrophages depend on the various signals coming from the tumour microenvironment. Whereas M1 macrophages produce significant quantities of pro-inflammatory Th1 cytokines, mediate resistance against pathogens and can kill tumour cells, M2 activation results in TAMs supporting pro-tumour functions with an $IL\text{-}10^{high}$, $IL\text{-}12^{low}$ phenotype [5,6]. Macrophages have substantial plasticity and given the extent of stimulation and context they can have many different phenotypes, and they are dynamic and they can change their polarization state [5]. The retinoic-acid-related

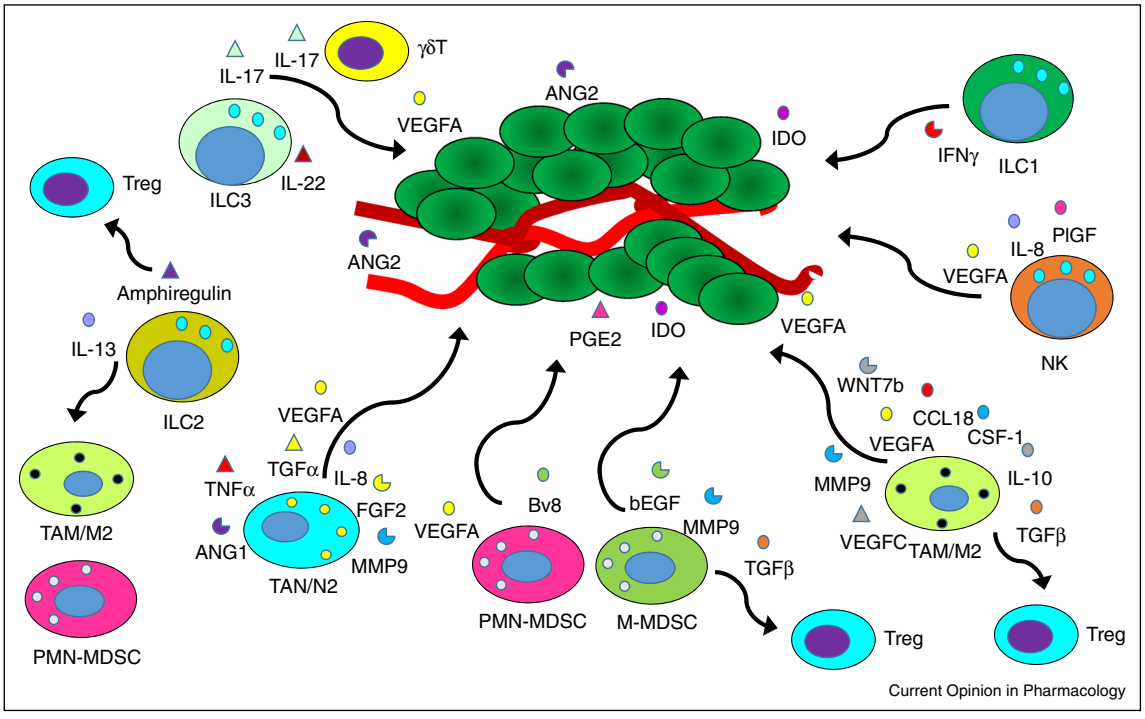
orphan receptor (RORC1/RORγ) promotes tumour progression by supporting TAM differentiation, M2 polarization as well as inhibiting MDSC apoptosis and infiltration of mature neutrophils [8••].

An interesting subset of TAMs/M2 macrophages is the perivascular macrophages that express high levels of Tie2 [9]. Experimental evidence has pointed out the role played by these cells in inducing chemotherapeutic drug resistance as well as modulating cancer cell responsiveness to radiotherapy [9,10]. After radiotherapy or chemotherapy, the recruitment and retention of monocytes and macrophages releasing pro-angiogenic cytokines and metalloproteinases induce angiogenesis within the tumour [9,10]. Irradiated human macrophages in the Matrigel invasion and chick embryo chorioallantoic membrane (CAM) assays promote cancer cell invasion and cancer cell-induced angiogenesis *in vitro* [11•]. Production of CCL18 by TAMs is associated with promotion of angiogenesis and tumour progression in breast cancer [12] (Figure 1). Breast cancer TAMs can also release WNT7b, a molecule that targets endothelial cells (ECs) inducing them to produce VEGF (Figure 1), thus enabling the angiogenic switch [13••].

Another key factor in the promotion of angiogenesis is the matrix metalloproteinase-9 (MMP9) that is released by TAMs [14] (Figure 1). MMP9 can play a determinant role in tumour angiogenesis and also in metastasis by turning on the angiogenic switch in avascular tumours [15]. Tumour-induced hypoxia induces VEGFA (angiogenesis), and VEGFC and VEGFD production by TAMs promotes lymphatic vessel formation, favouring lymphangiogenesis and metastasis [6,16–18].

TAMs could be responsible for maintaining the immunosuppressive tumour microenvironment in synergy with the action of MDSCs, tumour-associated dendritic cells, and neutrophils [5,6]. These cells secrete chemokines, such as CCL5, CCL22, and CCL20 able to recruit Treg cells, as well as cytokines such as IL-10 and TGFβ, resulting in the induction of Treg cells. TAMs are also responsible of inhibition of different chemotherapeutic agents by several mechanisms. For example in mammary cancers they induce chemotherapeutic drug resistance via IL-10/STAT3/Bcl-2 signalling pathway [19]. TAMs are associated with inhibition of action of novel treatments such as the epidermal growth factor receptor tyrosine kinase inhibitors for advanced lung adenocarcinomas [20].

Figure 1



Different pro-tumour pro-angiogenic roles by tumour infiltrating immune cells. Tumour microenvironment can shape and influence the phenotype and function of innate immune cells rendering them active protagonists in the tumour progression, angiogenesis, lymphangiogenesis, and invasive processes. The intimate interplay between tumour cells, stromal cells, endothelial cells and immune tumour-polarized cells leads to malignancy. Among these cells, TAM/M2, PMN-MDSC, M-MDSC, TAN/N2, Treg, γδT, ILC1 (NK), ILC2, and ILC3 cells interact each other and with tumour cells by their soluble products which can render the growing cancers refractory to the anti-tumour effects of innate and adaptive immune cells and stimulates angiogenesis and lymphangiogenesis, leading to invasion and metastasis.