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Review Article

The role of macrophages in bone metastasis

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ABSTRACT

The skeleton is one of the most common sites of metastatic disease, affecting a large number of patients with advanced cancer. Although an increasing number of therapies are available for treatment of bone metastasis, this remains incurable, highlighting the need for better understanding of the underlying biology. Metastatic tumour spread to distant organs is a multistage process, involving not only cancer cells but also those of the surrounding host microenvironment. Tumour associated macrophages are multifunctional cells that contribute both to tumour development and response to treatment by regulating adaptive immunity, remodelling of stroma, mediating basement membrane breakdown and angiogenesis. Although direct evidence for a specific role of macrophages in bone metastasis is limited, their involvement in metastasis in general is well documented. In this review we provide an overview of role of macrophages in tumour progression, with particular emphasis on their potential role in bone metastasis.

1. Introduction

The skeleton is a common site of metastatic disease, affecting a large number of patients with advanced cancer [1]. Around 70% of patients who die of prostate and breast cancer concurrently experience bone metastasis and the incidence in kidney, thyroid and bronchus carcinomas reported to be around 30–40%. In contrast, tumours of the gastrointestinal tract rarely metastasise to the skeleton (~5%) [2].

Metastasis to bone usually signifies an increased morbidity due to skeletal-related events, including bone pain, nerve and spinal cord compression syndrome, hypercalcaemia and pathologic fractures. As a result, the quality of life of the affected individuals may be greatly diminished [1]. Despite significant improvements in the outcome of patients with organ-confined cancer, patients with metastatic disease have not shared the same advances [3]. In an effort to maintain quality of life, improve survival as well as increase therapeutic options available for patients with bone metastasis, the underlying mechanisms should be investigated and understood.

A number of complex steps are involved in the formation of bone metastasis, involving a myriad of interactions between different cell types in conjunction with a large number of soluble factors, extracellular matrix components, hormones, physical properties [3]. Increasing evidence suggest that macrophages contribute both to primary tumour growth and to the subsequent development of metastasis [4]. However, there is very limited evidence for a specific role of macrophages in development and progression of bone metastasis. In this review we will give a brief overview of the current understanding of the contribution of macrophages to cancer metastasis, with particular emphasis on the involvement in tumour spread to the skeleton.

2. Macrophages

2.1. Macrophage classification and subtypes

Macrophages differentiate in tissues from extravasating monocytes and form an important component of the immune system characterised by their multifunctional nature. Monocytes are members of the family of leucocytes originating in the bone marrow, and they share a common progenitor with eosinophils, neutrophils and mast cells among others. Monocytes circulate for several days in the bloodstream where they are first released, followed by their entry into tissues where they replenish the tissue macrophage population [5].

Cells that belong to the monocyte/macrophage lineage are defined by their plasticity and heterogeneity, and their phenotype can be altered and adapted according to their resident microenvironment [6]. Macrophages are classified into M1 and M2 types, reflecting the Th1/Th2 nomenclature (see Fig. 1 and Tables 1). M1, or classically activated macrophages, are promoted by 'classical activators', such as interferon γ and lipopolysaccharide [7]. They are characterised by high IL-23 and IL-12 production, high capacity for antigen presentation and eventual activation of

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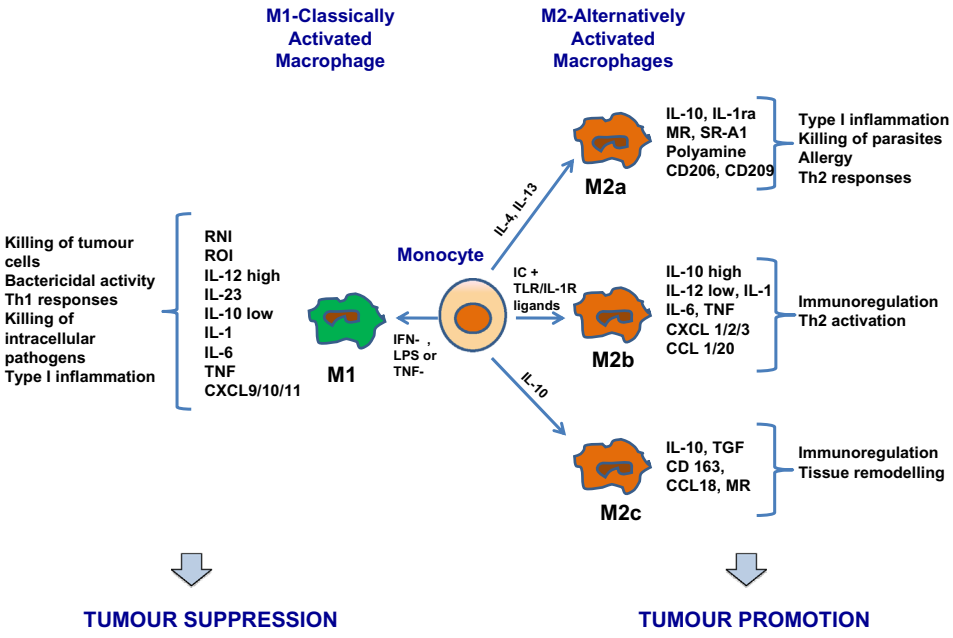

Fig. 1. Macrophage polarization. Exposure to different cytokine milieu promotes the differentiation of monocytes into polarised macrophage subsets. When exposed to LPS, IFN-γ or other microbial products, monocytes differentiate into M1 macrophages. When exposed to IL-4, IL-10, IL-13 and immuno-suppressive agents, monocytes differentiate into M2 macrophages. M1 and M2 subsets share different characteristics in their function and phenotype. M1 cells have bactericidal activity, immuno-stimulatory functions and display tumour cytotoxicity. M2 cells promote tissue repair and angiogenesis and have high scavenging ability, favouring tumour progression. Abbreviations are: RNI, reactive nitrogen intermediates; ROI, reactive oxygen intermediates; IL, interleukin; TNF, tumour necrosis factor; CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; LPS, lipopolysaccharide; IC, immune complexes; TLR, toll-like receptor; MR, mannose receptor; SR, scavenger receptor; CCL, CC chemokine ligand; TGF, transforming growth factor.

Table 1
Characteristics of M1, M2 and TAM. Different macrophage phenotypes share different characteristics in terms of polarising signals, membrane receptors, cytokines and chemokines released and function. The most commonly used markers for each macrophage type is given.

	M1-classically activated macrophages	M2-alternatively activated macrophages	TAM-tumour-associated macrophages	References
Polarising signals	IFN-γ, LPS or TNF-a	IL-4, IL-13 (M2a), IC+TLR/IL-1R Ligands (M2b), IL-10 (M2c)	CSF-1, VEGF, CCL2/3/4/5/8, IL-4, IL-13, IL-10, TGF-β, PGE_2	[4,9,10]
Membrane receptors	TLR2, TLR4, CD16, CD32, CD64, CD80, CD86	Scavenge receptor A/B, CD 14, CD 23, CD 163, MR	CD11b, CD45, F4/80 (mice), CXCR4, Gr1,CD68, VEGFR	[4,9,10]
Cytokines released	High IL-12, IL-23, low IL-10, IL-1, TNF, IL-6, ROI, RNI	High IL-10, low IL-12; TGF-β (M2c); low IL-1, TNF, IL-6 (not M2b); high decoy IL-1RII, IL-1R-antagonist, EGF, FGF, VEGF, TNF-β	FGF, PDGF, EGFR, VEGF, ANG1/2, IL-1/8, TNF-α, TP, MMP-2/9, CSF-1	[4,9,10]
Chemokines released	CXCL 8/9/10/11/16 CCL2/3/4/5	CCL 1/16/17/18/22/24	CCL-2/3	[4,9,10]
Function	Th2 responses, type II inflammation, allergy, killing and encapsulation of parasites	Th2 activation, immunoregulation, matrix deposition and tissue remodelling	Angiogenesis, tumour growth, tumour invasion, intravasation, immunosuppression, metastasis	[4,9,10]
Markers (mouse)	iNOS, CD197	Arginase-1, CD163	F4/80	[4,9,10]

Abbreviations are: IFN, interferon; LPS, lipopolysaccharide; TNF, tumour necrosis factor; IL, interleukin; IC, immune complexes; TLR, toll-like receptor; CSF, colony stimulating factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; CCL, CC chemokine ligand; TGF, transforming growth factor; PGE, prostaglandin E; ROI, reactive oxygen intermediates; RNI, reactive nitrogen intermediates; EGF, epidermal growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; EGFR, epidermal growth factor receptor; ANG, angiopoietin; MMP, matrix metalloproteinase; CXCL, chemokine (C-X-C motif) ligand.

polarised Th1 responses [8]. Cytotoxicity against tumour cells, as well as towards cells that have ingested intracellular microorganisms, is a key feature of M1 macrophages, mediated by the release of TNF, nitric oxide and reactive oxygen intermediates [4]. The involvement of M1 macrophages in the adaptive immune system is highlighted by the production of copious amounts of proinflammatory and immunomodulatory cytokines [9].

M2, or alternatively activated macrophages, are induced by IL-4, IL-10 and or IL-13 [7]. M2 is a broad name given to several forms of activated macrophages, excluding classic M1 cells, but including cells exposed to IL-13 or IL-4, IL-10, immune complexes, serocosteroid hormones and glucocorticoid [10]. Their main characteristics are suppression of inflammatory responses, poor antigen capacity and stimulation of Th2 responses [8]. They have been extensively shown to promote angiogenesis, wound healing and tissue remodelling, as well as to scavenge debris [8]. M2 macrophages are further categorised into M2a, M2b and M2c subtypes, depending on the environmental signals that define their activation. M2c is the most immunosuppressive of these phenotypes [9]. However, the different macrophage phenotypes are not considered distinct entities due to the degree of overlap between them, making their separation rather difficult and tentative.