Tumour Blood Vessels

Subjects: Oncology

Contributor: Yang Zhao

Tumour blood vessels, characterised by abnormal morphology and function, create an immunosuppressive tumour microenvironment via restricting the appropriate leucocyte subsets trafficking. Strategies to trigger phenotypic alteration in tumour vascular system to resemble normal vascular system, named vascular normalisation, promote effective trafficking of leucocytes into tumours through enhancing the interactions between leucocytes and endothelial cells.

Keywords: tumour vasculature ; leucocyte trafficking ; vascular normalisation ; immunotherapy

1. Introduction

The presence of specific subtypes of leucocytes in tumours is closely related to improved prognosis for cancer patients [1]. The ability of leucocytes to perform immune surveillance relies on their potential to infiltrate into the tumour, and penetrate into the tumour parenchyma [2]. The tumour endothelium is recognised as a hub for controlling the trafficking of leucocytes into solid cancers. As for a normal inflammatory or immune response, leucocyte trafficking occurs through a multiple cascade of events starting with leucocyte capture onto the tumour endothelial cells (ECs), their rolling and firm adhesion on the activated endothelium, intraluminal crawling of the leucocytes, and finally their transmigration across the endothelial barrier. This transmigration can occur via either the paracellular route generated between two adjacent ECs, or the transcellular route, through the EC cell body [3][4]. Targeting tumour endothelium to enhance selective recruitment of leucocyte subsets to convert a ‘cold’ tumour to a ‘hot’ tumour may represent an effective avenue to improve immunotherapy and hence combat tumour progression.

The imbalance of angiogenic mediators in tumours is prone to strengthen tumour angiogenesis and elicit the tumour blood vessels to develop abnormally, in terms of structure and function. The aberrant tumour vasculature plays an important role in generating an immune suppressive microenvironment, preventing the trafficking of leucocytes from infiltrating into the tumour bed. Anti-angiogenesis therapy can result in altered leucocyte trafficking to enhance immunotherapy. However, the overall clinical achievement of anti-angiogenic agents has been less than what was expected. This lack of benefit for cancer patients appears to be due to “intrinsic resistance” (resistance to anti-angiogenic therapies observed at the beginning of the treatment) and “acquired resistance” (produced resistance after an initial response to anti-angiogenic therapies) to the drugs [5]. In recent years, vascular normalisation, defined as reversing abnormal tumour blood vessels back to normal blood vessels, has gained increasing attention due to its potent efficiency and limited side effects. It can restore the angiogenic vessels towards a mature and stable vasculature with improved vascular perfusion and reduced vascular permeability, offering an appropriate microenvironment for promoting the trafficking of leucocytes [6]. Notably, normalised tumour blood vessels can selectively control the infiltration of leucocyte subpopulations, enhancing the anti-tumour immunity [7].

2. Trafficking of Leucocytes in Tumour Blood Vessels

Leucocytes use an array of cell adhesion molecules and chemokines to attach and transmigrate across ECs in order to penetrate into connective tissue stroma at an inflammatory site [3]. The process proceeds from tethering (capture), followed by rolling, adhesion, intraluminal crawling and is completed by paracellular or transcellular migration across the endothelium [8]. The transient interaction between leucocytes and ECs as well as the impact of blood flow elicits the rolling of leucocytes on the apical EC surface, giving rise to pulling of long membrane tethers at the rear of the rolling leucocytes. Chemokines and other chemoattractants expressed on the EC surface are able to induce the activation of rolling leucocytes. The EC–leucocyte interaction induced by critical adhesion molecules governs firm adhesion and further crawling of the leucocytes until they transmigrate across the endothelial barrier [9][10].

Tumours demonstrate specific tumour microenvironments characterised by differential chemokines and chemotactic factors that affect leucocyte recruitment [11]. Leucocytes migrate in a directed manner along the concentration gradient of the chemokine or chemoattractant towards the inflammatory site. In tumours, these processes are aberrant, resulting in

either reduced or skewed leucocyte subset accumulation into the tumour parenchyma [1][12][13][14][15]. Nonetheless, tumours also appear to be diverse regarding the expression of molecules involved in leucocyte trafficking (homing-associated molecules). Some tumours present quite an inflammatory type of endothelium with high levels of adhesion molecules expression, and this has been deemed to have a prognostic impact [16].

Leucocytes, or white blood cells (WBC), exert fundamental effects on the human immune system. They can be divided into three main subpopulations: lymphocytes, monocytes, and granulocytes. The overall survival of cancer patients is correlated with type and level of leucocyte subpopulations in the tumour parenchyma, with good survival associated with $CD8^+$ T cells, NKs, and DCs, and poor survival associated with neutrophils, Tregs, etc. Thus, efficient admission to these well-defined leucocyte subpopulations presents conspicuous value in research as well as in clinical applications [17][18]. In the tumour setting, selective control of leucocyte trafficking plays a key role in the establishment of effective immune responses against tumour cells [19]. Although targeting the composition and the metabolic state of tumour-associated leucocytes has been proposed as a possibility in altering leucocyte trafficking, emerging evidence has suggested that the regulation of tumour blood vessels may represent a new promising intervention strategy [20].

3. Conclusions

The goal of immunotherapy is to harness the immune response to deliver tumour killing potential. However, the immune suppressive nature of the tumour microenvironment hinders the infiltration of leucocytes into tumour parenchyma. Thus, strategies for converting “cold tumours” into “hot tumours” as evidenced by increased and appropriate leucocyte infiltration into tumour parenchyma, have gained attention. Since blood vessels, and in particular the endothelium, are central players in controlling the delivery of leucocytes into tissue, it has become a new target for anti-cancer therapies. Indeed, anti-angiogenic treatment can promote leucocyte trafficking and reduce the number of newly formed blood vessels. Further, vascular normalisation as a novel vasculature-targeting therapy facilitates the trafficking of leucocytes via improving tumour vascular structure and function. Of particular note now are strategies that will enhance selective immune subsets and will aid their activation while inhibiting access of detrimental subsets into the tumour to improve cancer immunotherapy and bring great benefit for cancer patients.

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