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Multifaceted effects of the microenvironment on tumour progression

Daniela F. Quail and Johanna A. Joyce

Tumours contain diverse cell types and inflammatory mediators within their microenvironment, such as tissue-resident and peripherally recruited immune cells, fibroblasts and endothelial cells, among others. Depending on the tissue type, there are unique variations in stromal composition, which can affect tumour progression in various ways. For example, brain tumours contain astrocytes, neurons and microglia, whereas breast tumours interact directly with adipocytes within mammary tissue. In addition to inputs from the local microenvironment, the systemic environment can also contribute to niche evolution by facilitating communication between different organ systems and can directly influence the survival of circulating tumour cells. Indeed, tumour progression is dictated not only by genomic events within tumour cells, but also by whether the surrounding niche is permissive to growth at all stages of disease. Thus, consideration of both tumour cell-intrinsic and -extrinsic mediators of disease progression is crucial to optimize current therapeutic strategies.

Initiation ▼

Under normal physiological conditions, cells within the microenvironment limit the establishment of the primary tumour (e.g. fibroblasts promote ECM homeostasis, pericytes serve as early gatekeepers of primary tumour growth and macrophages exhibit anti-tumorigenic behaviour). However, successful tumour progression necessitates evasion of these suppressive functions, often by hijacking cells in the microenvironment (e.g. FAP$^+$ fibroblasts become immunosuppressive, pericytes cause recruitment of MDSCs, macrophages are reprogrammed to become pro-tumorigenic and mast cells accumulate in number). This occurs in conjunction with increases in tumour proliferation and hypoxia, aberrant inflammation and angiogenesis. In cases where the microenvironment is already altered (e.g. in response to obesity, colitis or smoking) a growth-permissive niche leads to increased risk and incidence of tumour initiation.

Primary progression ▼

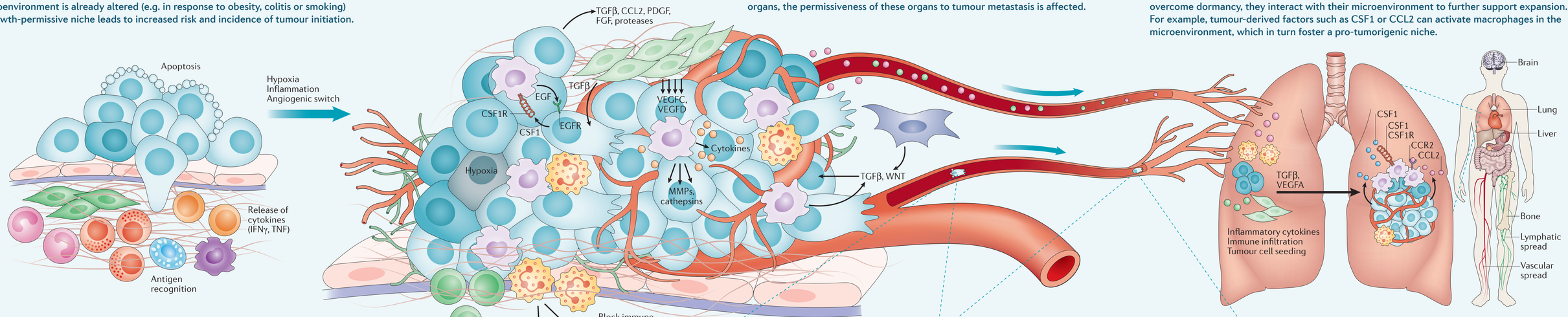
As tumour cells adopt invasive and immunosuppressive phenotypes, they infiltrate the local tissue and disrupt homeostasis by releasing pro-tumorigenic factors, such as TGFβ, CCL2, PDGF, FGF and various proteases, into the microenvironment. These factors change the local milieu and affect the phenotype of surrounding cells, such as cancer-associated fibroblasts and macrophages.

Systemic communication ▼

Tumours release factors into circulation (e.g. cytokines, growth factors and exosomes), which can not only affect tumour cell survival within the blood, but may also prime the pre-metastatic niche before the arrival of disseminating tumour cells, cause changes to the cellular landscape within the secondary organ and support outgrowth once metastatic tumour cells have colonized. Inter-organ communication can also contribute to this systemic milieu to ultimately impact homeostasis within different organs. For example, adipose tissue can secrete cytokines into the circulation to affect immune infiltration into various tissues including liver or lung. By altering the stromal landscape within secondary organs, the permissiveness of these organs to tumour metastasis is affected.

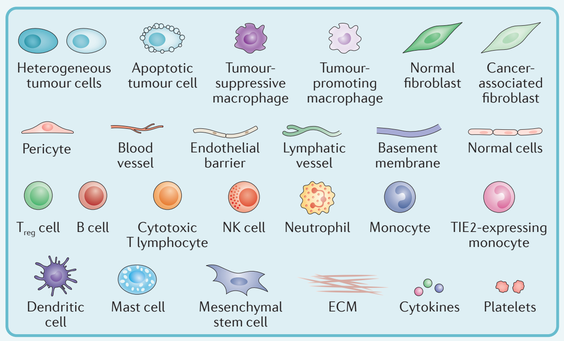
Secondary colonization and progression ▼

Once tumour cells arrive in secondary tissues, the microenvironment must be permissive to their colonization and expansion for overt disease to develop. For example, neutrophils have been shown to play a crucial role during colonization of lung metastases, by secreting growth factors and leukotrienes into the microenvironment to create selection pressure for clones with high tumorigenicity, or by suppressing cytotoxic immune cells such as CD8$^+$ T cells or NK cells. Fibroblasts are also important as they contribute to ECM composition (e.g. through periostin production). Micrometastases can remain dormant within secondary tissues or undergo secondary progression to overt disease. Tumour mass dormancy can be maintained by immune surveillance and/or lack of vasculature-supplied nutrients. Once micrometastases overcome dormancy, they interact with their microenvironment to further support expansion. For example, tumour-derived factors such as CSF1 or CCL2 can activate macrophages in the microenvironment, which in turn foster a pro-tumorigenic niche.



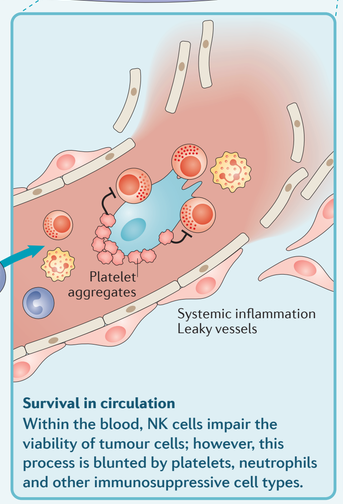
Immunosuppression ▶

Suppressor cells such as MDSCs, neutrophils or T_{reg} cells block the antitumour functions of antigen-presenting cells (e.g. dendritic cells), T_H1 immunity, B cells, etc.



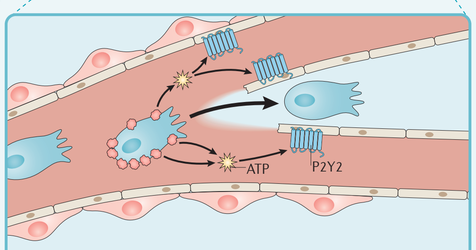
Inflammation and immune recruitment ▲▶

Immune cells within the tumour are either tissue resident or derived from peripheral sources. Some tissue-resident immune cells, such as microglia within the brain, are formed during embryonic development, whereas infiltrating immune cells are generated by haematopoiesis from bone marrow progenitor cells. Immune cells that are released into circulation can be further primed within the lymph nodes and/or target tissues, or can home to reservoirs such as the spleen until they are stimulated for release.



Survival in circulation

Within the blood, NK cells impair the viability of tumour cells; however, this process is blunted by platelets, neutrophils and other immunosuppressive cell types.



Extravasation

Tumour cells can co-opt physiological processes associated with vascular injury, to successfully cross vessel barriers. For example, platelets can mediate tumour cell aggregation and attachment to the endothelium through integrin interactions, reminiscent of clotting. Platelets can additionally support extravasation at secondary organs through ATP-dependent activation of endothelial cells expressing the P2Y2 receptor. This causes the endothelium to open transiently and thereby enables metastatic seeding. Endothelial cells can acquire different phenotypes, for example, through altered HIF or Notch signalling, to affect the efficiency of this process.

Microenvironment-targeted therapies

Targeting myeloid cells
- Macrophage re-education or depletion through CSF1R blockade
- Blockade of cytokine gradients to impede myeloid cell recruitment
- Neutralization of TIE2-expressing monocytes to reduce tumour vascularity

Targeting lymphoid cells
- Dendritic cell vaccination to enhance T cell responses
- Increase expression of stimulatory checkpoint molecules on antigen-presenting cells
- Blockade of inhibitory checkpoint molecules (e.g. CTLA4, PD1 and PDL1) to boost T cell co-stimulation

Targeting the vasculature
- Inhibition of angiogenesis regulators, such as VEGF ligands or receptors
- Reduction of growth factor availability through VEGF–Trap

Targeting the environment
- Manipulation of ECM stiffness and fibrosis to improve drug delivery
- Improving oxygenation through vascular normalization
- Lifestyle interventions, such as weight loss, to improve systemic immune function

Abbreviations
CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CSF1, colony stimulating factor 1; CSF1R, CSF1 receptor; CTLA4, cytotoxic T lymphocyte associated antigen 4; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, EGF receptor; FAP, fibroblast activation protein; FGF, fibroblast growth factor; HIF, hypoxia-inducible factor; IFNγ, interferon-γ; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloproteinase; NK, natural killer; P2Y2, P2Y purinoceptor 2; PD1, programmed cell death protein 1; PDGF, platelet-derived growth factor; PDL1, PD1 ligand 1; TGFβ, transforming growth factor-β; T_H1, T helper 1; TIE2, angiopoietin 1 receptor; TNF, tumour necrosis factor; T_{reg}, regulatory T; VEGF, vascular endothelial growth factor.

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