Inflammation in cancer and the role of Tumor-associated Macrophages

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Introduction

Cancer is a group of diseases characterized by uncontrolled growth cell and the spread of abnormal cells that causes approximately 8 million deaths every year. There is still no general cure for cancer and the exact role of inflammatory cells and mediators remains unknown. Tumor-Associated Macrophages (TAMs) represent up to 50% of tumor mass and they are the main inflammatory cells that promote the growth of a great number of cancers [1]. TAMs are the most important cells in the connection between inflammation and cancer carrying out an important number of functions that have a crucial impact on cancer progression: tumor promotion, down-regulation of adaptive immunity and metastasis. Therefore, TAMs enhance the development of tumor and represent an attractive target for novel tumor biological therapies.

Abbreviations: IL= interleukin, ECM= extracellular matrix, VEGF= vascular endothelial growth factor, PDGF= platelet-derived growth factor, TNF-α= tumor necrosis factor-alpha, DC= dendritic cell(s), TGF-β= transforming growth factor-beta, MMPs= matrix metalloproteinase, Th1= T-cell CD4+ Th1, Th2= T-cell CD4+ Th2, HIF-1= hypoxia-inducible factor-1; Treg= regulatory T-cell.

1. Inflammation and cancer

Tumors are originated through mutations that can be produced by chronic inflammation or by endogenous processes such as errors in replication. Whatever the origin of the tumor is, inflammatory cells are present from the earliest stages of development [2]. In this stages, tumor cells produce several cytokines and chemokines (such as CCL2 and CCL5). This production results in inflammatory cells being recruited from blood to the tumor and they also begin to segregate inflammatory mediators.

As shown in figure 1, monocytes can differentiate towards macrophages M1 or M2. Macrophages can inhibit or promote all aspects of tumor development depending on the composition of the tumor microenvironment, which guides their differentiation. The presence of anti-inflammatory cytokines, such as IL-4, IL-10 and IL-13, switches monocytes differentiation towards macrophages M2 (pro-tumoral phenotype) whereas pro-inflammatory cytokines switch their differentiation towards macrophages M1 (anti-tumoral phenotype). TAMs have an M2 phenotype.

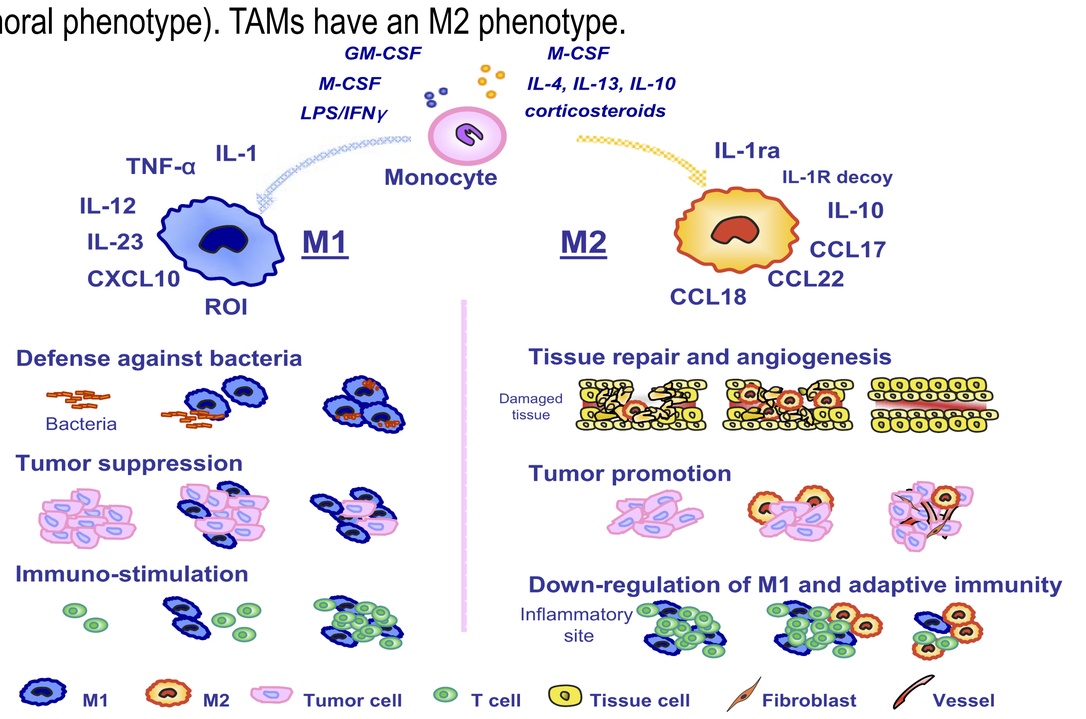

Figure 1: The differentiation pathways of monocyte towards classically-activated M1 macrophages and alternatively-activated M2 macrophages. M1 macrophages act as soldiers: they defend the host from viral and microbial infections, fight against tumors, produce high amounts of inflammatory cytokines and activate the immune response. In contrast, M2 macrophages (TAMs) promote tumor in several aspects: tumor cell survival, proliferation and dissemination. They also suppress the anticancer activity of immunological system.

2. Tumor-associated macrophages

TAMs produce many factors that promote tumor cell survival, metastasis and down-regulation of adaptive immunity (Figure 2) [3].

TAMs are preferentially localized in tumor hypoxic regions. They promote an overexpression of proangiogenic molecules (ex. VEGF, PDGF) by HIF-1 activation. Moreover, in tumors there is an established gradient of IL-10, which switches monocyte differentiation towards macrophages rather than DC and also, indirectly, induces naïve T cells anergy [2]. CCL17, CCL22 and CCL18 also contribute to down-regulate adaptive immunity as well as TGF-β which in turn promotes proliferation of tumor cells (Figure 2). Metastasis is favored by MMPs, proteases, IL-1β and TNF-α. All together, they act on cell-cell junctions modifying the ECM composition and promoting the disruption of the basal membrane. Besides, TAMs contribute actively to build up the tumor matrix architecture by producing several matrix proteins which modulate collagen density, leukocyte and blood vessel infiltration [1].

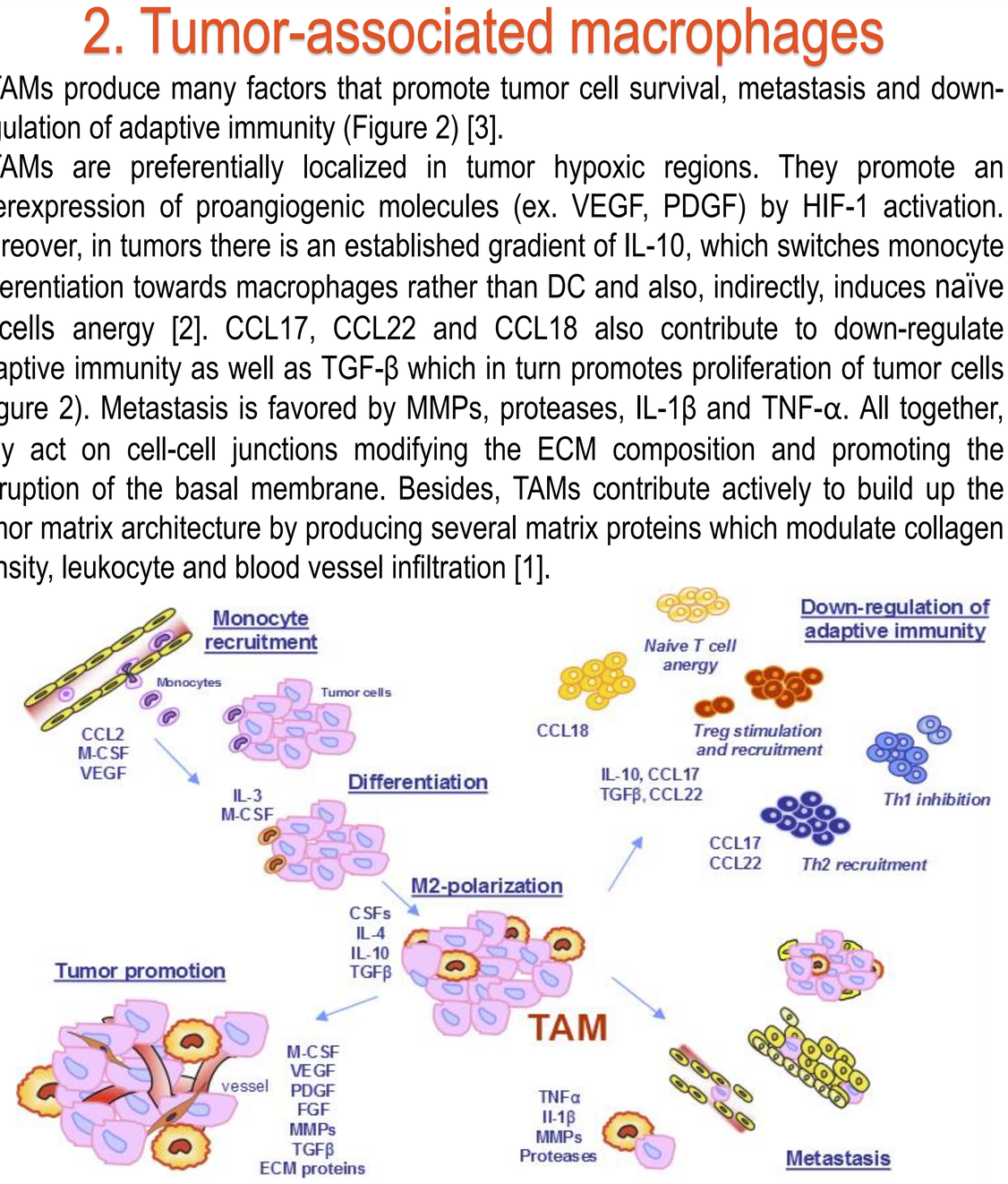

Figure 2: Overview of how monocytes are recruited, differentiated and M2-polarized and how TAMs induce the progression of the necrotic tissue. They produce several molecules that sustain malignant cell survival, modify neoplastic ECM proteins, promote the development of a newly formed vessel and assist tumor cells in their progression. Moreover, TAMs down-regulate adaptive immune responses significantly by recruiting Tregs (which are also stimulated) and Th2 lymphocytes, which in turn inhibit Th1 cells, and by inducing anergy of naïve T cells.

3. Anti-cancer immunotherapies

Novel anti-cancer immunotherapies consist of blocking the main pro-tumor factors secreted by TAMs with antibodies in order to inhibit either the monocyte recruitment, the TAMs activation, the tumor promotion or the metastasis. This is illustrated in Figure 3.

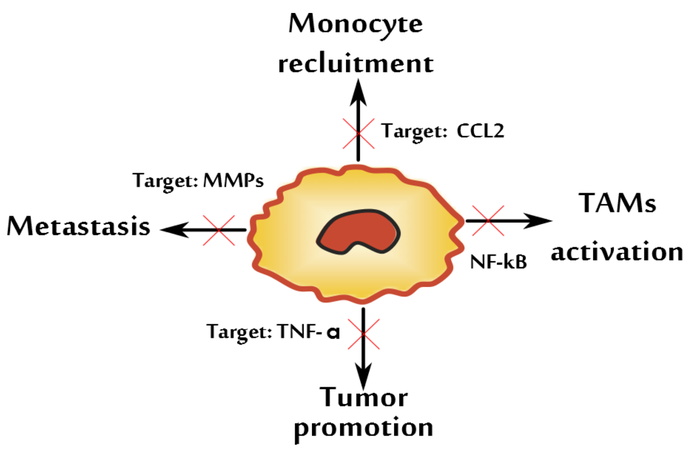

Figure 3: Possible immunotherapies strategies to block the main pro-tumor factors.

NF-kB is a transcription factor very active in TAMs. It induces several cellular modifications associated with tumorgenesis and aggressive phenotypes, including self-sufficiency in growth signals and insensitivity to growth inhibition, resistance to apoptotic signals, angiogenesis, migration and tissue invasion. Moreover, constitutive NF-κB activation is often observed in cancer cells.

Conclusions

- ❑ TAMs are key orchestrators of cancer- related inflammation.
- ❑ Neoplastic cells actively guide monocyte recruitment from blood into tumor tissues to their own advantage. They produce many growth factors for tumor cells and for the nascent blood vessels, essential for tumor growth.
- ❑ TAMs actively participate in metastasis and in the suppression of the adaptive immune response that could potentially attack tumor cells.
- ❑ Anti-tumor activity can be achieved by targeting recruitment, survival and polarization of TAMs as well as their activities.
- ❑ Therapeutic targeting of macrophages in humans may represent a valuable strategy to complement conventional anticancer strategies.

References

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[3] Macrophage polarization: tumor associated macrophages as a paradigm for polarized m2 mononuclear phagocytes. Trends immunol 23, 549-555.
Figures 1 and 2 come from [1].