MACROPHAGES AS A KEY FACTOR IN THE PROCESS OF TUMOUR FROM THE INITIATION TO THE THERAPY OF CANCER.

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ABSTRACT

The tumor environment is a complex ecological system made up of cells and serves as support to the tumor cells from their implantation to the state of malignancy. Among all the cells of immunity (innate and adaptive) macrophages are those most present on the site of the tumor, playing a predominant role in all stages where they intensively promote the different aspects of tumor initiation, growth and development. Macrophages are composed of two subpopulations M1 (anti-tumor, responsible of the inflammation response and pathogen clearance) and M2 (pro-tumor and anti-inflammatory activities) both depending of diverse external factors. Clinical studies and experimental models have shown that tumor associated macrophages (TAMs) are more related to the M2, giving a poor clinical prognostic by promoting the growth of the tumor and assessing a favorable microenvironment to the malignancy. Thus, this ability to promote tumor proliferation makes these TAMs a key tool targets for curative cancer solutions via translational approaches, but more research need to be done to ensure a better prognosis.

KEYWORDS: Macrophages M1/M2, tumor associated macrophages, macrophage polarization, Cancer, immunotherapy.

1-INTRODUCTION

Macrophages are innate immune cells that play a broad role in host defense and the maintenance of tissue homeostasis.[1] Tissue-resident and inflammatory macrophages
originate from circulating bone marrow-derived monocytic precursors.\[^2\]\ The complex microenvironment of the tumor involves since its initiation, a large number of malignant and non-malignant cells as well as cancer cells with Stroma and some of the host cells. Where they all interact to promote the growth of the tumor in a synchronic way. The tumoral environment is composed of fibroblasts, endothelial cells and complex inflammatory infiltrates, containing different cells of the haematopoietic system (neutrophils, monocytes / macrophages). Monocytes are known to originate in the bone marrow from a common myeloid progenitor that is shared with neutrophils, and they are then released into the peripheral blood, where they circulate for several days before entering tissues and replenishing the tissue macrophage populations.\[^3\]\ Tumor associated macrophages (TAMs) constitute a major part of the leukocytes infiltrate in human cancer. Substantial evidence indicates that macrophages rather than being tumoricidal as suggested after their activation in vitro.\[^4\]\ adopt a pro-tumoral phenotype in vivo both in the primary and metastatic sites.\[^5\]\ For example, lung cancer macrophages are polarized to a pro-tumoral phenotype at the time of tumor initiation.\[^6\]\ These precursor cells extravasate into target tissues where they differentiate into mature macrophages and polarize into diverse subsets that have different phenotypes in response to micro-environmental challenges.\[^7\]\ These activities include suppression of T cell responses.\[^8,9\]\ In addition, macrophages promote many important features of tumor progression including angiogenesis, tumor cell invasion, motility and intravasation as well as at the metastatic site, stimulation of tumor cell extravasations and persistent growth.\[^9\]\ Each of these activities is delivered by an identifiable sub-population of macrophages.\[^9\]\ Furthermore, it has been estimated that 80% of studies that have tried to relate TAM density to prognosis in any type of cancer have found a negative correlation while less than 10% have found a positive correlation.\[^10, 11\]\ The inhibition of tumor and metastasis progression by the ablation of macrophages as shown by several experiments and data proving that the presence of immune cells is very important for the tumor development which can lead to a malignant state or more deeply their acquisition of a malignant phenotype. Which could therefore be a potential target in the search for a curative solution of cancer. Thus, the purpose of this review will discuss the function of diverse macrophage subpopulations showing how the tumor microenvironment takes advantage of macrophage plasticity to mold an immunosuppressive population and their dynamic interplay with tumor cells that confer these pro-tumoral activities and give particular emphasis to the immunoregulatory role of these cells.
2- MACROPHAGES

Macrophages are monocyte-derived myeloid cells that develop from a common myeloid progenitor cell residing within the bone marrow of adult mammals [12]. This will also give rise to other myeloid cells, specifically neutrophils, eosinophils, basophiles and dendritic cells, all of which will be exposed to cytokines during their maturation. Like others, the monocytes are derived from this same progenitor site, this during a cascade of events involving granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF) and macrophage colony stimulating factor (M-CSF), leading to a differentiation of hematopoietic stem cells into monoblasts, pro-monocytes and finally into monocytes. Mature monocytes leave the nest to the bloodstream for about 1-3 days and finally enter the different tissues and become macrophages for a steady-state renewal process or due to chemotactic attractants produced in the framework of a local inflammatory treatment. Prior to entering tissues and differentiating into macrophages, circulating blood monocytes are known to be heterogeneous with at least two general populations identified.[13,14,15] Among which CD14hi, CD16- and CD14+, CD16+ in humans, Ly6Chigh (GR1+) with Ly6Clow (GR1-) in mice. These phenotypes are respectively divided into two groups: inflammatory (CD14hi, CD16 / Ly6Chigh) with the ability to migrate to the lesion or infected site mediated by the ligand C-C chemokine CC (CCR) 2-chemokine CC and to spread chronic inflammatory diseases and the group of resident who patrol the vascular system, regulate the inflammatory system and stay in the tissues. The gene expression of each macrophage population is related to the specific microenvironment of tissue in which they reside.

Essential markers of the state of health, macrophages derived from innate immunity and are known to be heterogeneous. There are two polarization states of the macrophages: Type 1 activated classically (M1) and type 2 (M2) “fig.1” The macrophages with M1 phenotype is adapted to attract and activate cells of the adaptive immune system in response of the danger signals delivered by bacterial products or interferon (IFNg). Important features of M1 macrophages are the expression of nitric oxide synthase (iNOS), reactive oxygen species (ROS) and the production of natural killer (NK) and type 1 T-cell stimulating cytokine IL-12. Beside M2 macrophages can develop in response to for instance IL-4 or IL-13.[16,17] M2 play a role in parasite clearance and wound healing where they also polarize T-cells to Th2 and dampen immune responses [18]. Even though less effective than dendritic cells, macrophages are antigen-presenting cells (APC) that express human leukocyte antigen (HLA) class I and class II molecules and co-stimulate / inhibit molecules to give instructions to T cells.
Macrophages display great plasticity and can adapt to a large number of activation states ranging between the M1 or M2 phenotype depending on the mix of signals in their direct microenvironment. In addition, fully polarized M1 and M2 macrophages can be redirected in vitro towards the opposite functional phenotype by treatment of the cells with cytokines.[19]

3- THE CONCEPT OF TUMOR ASSOCIATED MACROPHAGES
Macrophages play a prominent role in the stroma and leukocyte compartment in malignancy, distinct macrophage subsets in cancer have been described.[20,21,22,23] Since macrophages in human cancer cannot be classified into activated classical macrophages of type M1 or alternatively activated as M2, they are called macrophages associated with tumors (TAM). Depending on their activation state, TAMs can present both pro-tumoral and anti-tumoral functions. Macrophage cells have an extreme functional plasticity enabling them to integrate and respond to different stimuli.[24] After establishing the mechanism of tumor progression, TAMs often express an M2-like phenotype, promote tumor growth through angiogenesis, tissue remodeling, suppression of adaptive immunity[25,26] and promote metastasis “fig.2”

4-MECHANISMS OF MACROPHAGE RECRUITMENT AND MACROPHAGE POLARIZATION IN TUMOR PROGRESSION
Macrophages are among the first immune cells to infiltrate the pre-invasive tumorous lesions and persist during the development into invasive cancer.[27] As has been shown in previous studies, cancer is associated with inflammation that leads to the recruitment of cells derived from bone marrow.[28,29]. Certain growth factors such as colony stimulating factor 1 (CSF-1), vascular epithelial growth factor (VEGF), but also monocyte, chemotactic protein 1 (MCP-1), many other chemokines CCL and other molecules induce chemotaxis of monocytes in the tumor microenvironment. An explicit study in three different murine tumor models (the BALB / C4T1 mammary tumor model, the BALB / c mammary adenocarcinoma TS / A model and the C57BL / 6 3LL lung carcinoma model) the inflammatory Ly6Chi monocyte subset was shown to be the TAM subsets in the tumor.[30]. With regard to the specific tumor, the molecules are secreted by the tumor cells themselves or the adjacent stromal cells. In cutaneous carcinogenesis, for example, a carcinogenic application induces a proliferation of fibroblasts which secrete monocyte chemotactant protein-1(MCP-1), resulting in chemotaxis of the macrophages. Neutralization of MCP-1 almost completely blocks this accumulation of macrophages in the tumor.[31] Vascular endothelial growth factor (VEGF), beside its strong angiogenic role, recruits monocytes into the tumor microenvironment and
blockade of VEGF by bevacizumab results not only in reduced vessel density, but also in reduced TAM infiltration.[32] Once on the site of the tumor, monocytes differentiate into macrophages under the influence of macrophage colony stimulating factor (M-CSF) and others factors derived from tumor cells result in the polarization of macrophages. In general the inducion of a TAM related phenotype has been brought in context with tumor cell derived mediators such as M-CSF[33], IL-4, IL-10, IL-6,[34,35] transforming growth factor β (TGF-β1), prostaglandin E2 (PGE2)[36,37], hyaluron fragments.[32], and the leukemia inhibitory factor (LIF)[38]. In cervical cancer, monocytes are skewed from a dendritic (DC) towards a macrophage phenotype by the production of PGE2 and IL-6 from tumor cells.[39,40]

Similarly, TAMs are derived from circulating monocytes or tissue-resident macrophages.[41] Cytokines, chemokines, extracellular matrix (ECM) components, and hypoxia are the multiple microenvironmental signals responsible for the mobilization of macrophages in tumor tissues.

4.1 SOLUBLE FACTORS MEDIATING MACROPHAGE MOBILIZATION INTO TUMORS

Recruitment of macrophages at the tumor site is mainly regulated by cytokines, chemokines and growth factors that are derived from tumor and stromal cells of its microenvironment. Monocytes/macrophages migrate toward inflamed tissues under the influence of CCL2 (MCP-1).[42,43] Experimental studies have revealed the CCL2-dependent infiltration of macrophages into tumors.[44] For example, systemic administration of CCL2-neutralizing antibodies in tumor-bearing mice or the short-hairpin RNA knockdown of CCR2 in the cancer cell lines significantly reduced tumor growth along with reduced TAM recruitment.[45]. Along with the chemokines, several cytokines such as colony-stimulating factor-1 (CSF-1) and endothelial monocyte-activating polypeptide II (EMAPII) have been implicated in the recruitment of monocytes into tumors.[45,46] Indeed, an elevated CSF-1 level correlates with marked macrophage infiltration in human metastatic breast cancer.[48] Xenotransplantation experiments have further demonstrated that tumor cells transected with CSF-1 gene exhibited an increase in TAM infiltration.[49] Some growth factors as well as vascular endothelial growth factor (VEGF), endothelin 2, and platelet-derived growth factor (PDGF) have also been reported to promote monocyte/macrophage recruitment.[50, 51] Within the dense tumor microenvironment, the orchestrated actions of these soluble factors can synergistically speed
up the mobilization of macrophages and the change of these cells to TAMs, which lead to promote alterations in the tumor microenvironment.

4.2 ROLES OF EXTRACELLULAR MATRIX (ECM) COMPONENTS AND THEIR FRAGMENTS IN MACROPHAGE RECRUITMENT

Strands of the structures in and are believed to play essential roles in the formation of ECM during an inflammatory reaction. After binding to high molecular weight hyaluronic acid (HA), vesicant also cooperatively improves the adhesion of leukocytes to these cables, suggesting that the per cellular HA complex provides suitable support for macrophage recruitment. Our recent study demonstrated the preferential engagement of immunosuppressive M2 macrophages in a tumor microenvironment. Extracellular Matrix (ECM) serves as a structural support for the infiltration of innate immune cells and hyaluronic acid (HA) which is his major component. De la Motte and colleagues have shown that cable-type ECM structures have been formed after extensive HA deposition on smooth mucosal muscle cells treated with poly (I: C); these structures have been implicated in adhesion and recruitment of monocytes through association with the CD44 HA receptor. Numerous HA-binding partners, such as the inter-α-inhibitor heavy chain (IαI), the tumor necrosis factor (TNF), stimulated gene 6 (TSG-6) and the vesicant HA-binding proteoglycan, are located along the rich in HA and vesicant.

It has been shown that certain ECM molecules and their proteolytic fragments acted as inflammatory stimuli for the recruitment of innate immune cells thus leading to pro-inflammatory action. For example, elastin fragments generated by macrophage-derived matrix metalloproteinase (MMP)-9/12 exhibit a monocyte chemotactic activity. On other hand, TAM-derived oncofetal fibronectin not only promotes cancer cell invasion but also stimulates monocyte migration. Soluble biglycan and its fragments act on macrophages to produce both TNF-α and macrophage inflammatory protein-2 (MIP-2) in a manner that is dependent on TLR2 and TLR4, and thereby play a positive role in macrophage recruitment and activation. Oligosaccharides generated by hyaluronidase-catalyzed digestion of high-molecular-weight HA also utilize both TLR2 and TLR4 to stimulate inflammatory gene expression in macrophages and act as an endogenous danger signal. Tumor-derived HA fragments have also been shown to promote the development of immunosuppressive M2 macrophages by triggering a transient early activation of monocytes.
4.3 MACROPHAGE RECRUITMENT INTO HYPOXIC AREAS
Several pieces of evidence have shown that advanced solid tumors exhibit hypoxic areas within the tumor mass and that a high number of TAMs accumulate in the avascular areas of a wide range of human tumors. VEGF-A, endothelin-2, and EMAII were involved in the Hypoxia induced by the recruitment of macrophages. The suppression of VEGF-A derived from the myeloid has reduced vascularization in solid tumors. When TAM reaches hypoxic areas, hypoxia directs them to a pro-tumorigenic phenotype by altering gene expression profiles. Hypoxia-inducible factor (HIF)-1α is a key transcription factor that regulates hypoxia-induced gene expression. HIF-1α also induces CXCL12 expression in direct proportion to the reduced oxygen tension at hypoxic sites.

5- MACROPHAGES IN CANCER INITIATION AND PROMOTION
There is a reason to believe that inflammation is the cause of many cancers. Mantovani and colleagues have called this the seventh hallmark of cancer and reviewed its characteristics as well as the epidemiological and infectious disease literature that supports this hypothesis. Direct experimental support demonstrates the role of inflammation in cancer initiation, for example in a mouse model of lung cancer, bronchial exposure with H.influenzæ lysate results in inflammation in the lung and an increase in tumorigenesis. Myeloid-specific ablation of intergrin αV also results in an ulcerative colitis that induces colonic tumors. Ablation in myeloid cells of stat3, a transcription factor which function suppresses inflammatory responses because it is a major target of immunosuppressive cytokine IL-10. causes inflammation in the colon. This is associated with abundant expression of TNFα and IL-6 by macrophages and results in a chronic colitis and invasive colonic adenocarcinoma. The causality of the inflammation in carcinogenesis in these studies comes from experiments in which suppression of the bacterial flora by antibiotic treatment reduces the inflammation and inhibits tumorigenesis. These data show that the immune system is normally in equilibrium but once the negative controls of immune responses are compromised, a persistent inflammatory response to normally normal organisms results. This inflammation in turn creates a tumor that settles gradually.

The inflammatory state in myeloid cells is controlled by the transcriptional factors NF-κB and stat3 that work in opposition to one another. NF-κB is a central transducer signals that cause inflammation downstream of TLR activation. In the inflammatory responses associated with cancer initiation, NF-κB signaling is essential for the inflammatory
Inhibition of this activity through ablation of IκB kinase α (IKKα) in myeloid cells in mouse models of intestinal cancer reduces inflammation and inhibits tumor progression.\(^{[78]}\)

The type of inflammation associated with increased cancer risk because of chronic infection or persistent irritation is often called “smoldering inflammation”.\(^{[79]}\) Activated macrophages are central to this type of immune response and work in concert with other immune cells.\(^{[80]}\)

NO reacts with peroxide to give nitrosoperoxycarbonate, and this reaction is a key of the chemistry of inflammation. This highly reactive compound and other products cause mutations in the adjacent epithelial cells\(^{[81, 82]}\). In addition, there is evidence that the inflammatory microenvironment also promotes genetic instability within the developing tumor epithelial cells.\(^{[83]}\) The mutations are fixed after replication of the epithelial cells in all cases, one which is stimulated by growth factors synthesized by the infiltrating or resident immune cells which include macrophages. These growth-promoting effects on tumors are caused by the production of IL-6 in hepatocellular carcinoma (HCC).\(^{[84, 85]}\) and TNFα.\(^{[86]}\) and IL-6 in colitis associated cancers.\(^{[87]}\) Interestingly, IL-6 synthesis in Kupffer cells in response to inflammation-induced liver damage is gender dependent with males who have increased risk of HCC having elevated levels. IL-6 is also required for the increased risk of HCC in female mouse models.\(^{[88]}\) However, once initiated and as the tumors progress toward malignancy, the macrophage phenotype changes from the “inflammatory” type to one that promote tissue formation during development.\(^{[89, 90]}\) In established tumors, NF-κB signaling is inhibited by the constitutive expression of p50 homodimers that negatively regulate NF-κB and the macrophages display the M2/trophic phenotype which reduce iNOS and TNFα expression.\(^{[91]}\) The blocking of the NF-kB function by the inhibition of IKKα in the cultured macrophages reduces the expression signature of the inflammatory gene and pushes the cells to the trophic / M2 type. This transition from stimulated to inhibited NFkB function between initiation and established tumor stages is poorly understood. The type “activated / trophic” macrophage is also found in cancers that appear in the apparent absence of inflammation, such as breast cancer, in which macrophages are recruited in benign tumors in large numbers as well as the tumor transition to malignancy.

**6-IMMUNOSUPPRESSIVE PROPERTIES OF TAMs**

Immunosuppressive functions of TAMs appear to be conflicting to the inflammatory tumor-microenvironment and the inflammatory properties of macrophages. Even though TAMs
produce several chemokines that are associated with inflammation in immunity against pathogens, under sterile inflammatory conditions in cancer these molecules exert a growth promoting influence on tumor cells. This effect might be due to STAT3 activation in TAMs opposing STAT1 driven Th-1 anti-tumor responses. Expression of MHC class II molecules on TAMs is actively down regulated by tumor cell derived TGF-β1, IL-10 and PGE2. The direct inhibition of immune responses by TAM has also been described. IL-10 and TNF-α in the tumor microenvironment induce the expression of programmed dead-ligand 1 (PD-L1) also called B7-H1 on the membrane of macrophages associated with tumors. Although naive T lymphocytes can be stimulated via PD-L1, his most important role is the inhibition of PD-1 receptor activated T lymphocytes. Allavena and Mantovani have demonstrated an additional indirect mechanism of creating an anti-inflammatory tumor medium, namely the recruitment of other non-inflammatory immunity cells into the microenvironment of tumors. In the same sense, CCL17 and CCL22 produced by TAMs are involved to primarily attract Th2 and Treg which are non-cytotoxic cells. Macrophage-derived CCL18 recruits rather naive T-lymphocytes that are primed under immune regulation conditions. In a murine model of colorectal cancer, it was found that F4 / 80 + TAM secretes large amounts of CCL20 attracting CCR6 + cells on the tumor side.

7-MACROPHAGES AND THE METASTATIC SITE
Cancer is considered to be a systemic disease, and primary tumors secrete factors that influence metastatic outcome at remote sites. When the tumor cells escape from the primary site, they pass through the lymphatic and / or circulatory system and eventually some establish at distant sites to create metastases. These sites vary depending on the cancer, for example in the breast; they mainly go to the bone then the lung and the brain. This process is essential to understand that 95% of deaths from solid tumors in developed countries are due to metastasis.

Monocytes/macrophages are essential metastasis promoters acting both to prepare sites and also to promote the extravasation, the survival and the persistent growth of metastatic cells. These niches are populated by CD11b+, VEGFR1+ myeloid cells whose recruitment is promoted by Lysyl Oxidase (LOX) and S110A and whose ablation inhibits the formation of these sites. Several other factors have been shown to be important for pre-metastatic niche formation, most recently, tumor derived exosomes that program the myeloid cells to be pro-
tumoral and pro-angiogenic through activation of the receptor tyrosine kinase MET.\textsuperscript{[105]} Platelets are also key elements in the formation of niches, which presumably deposit fibrin in the target tissues to attract the myeloid cells. Thus, pre-metastatic niche formation is blocked by anticoagulants. Gil-Bernabe and colleagues found that tumor-derived tissue factor (coagulation factor III or CD142) stimulated clot formation and enhanced subsequent tumor cell survival at the metastatic site by recruiting CD11b\textsuperscript{+}/CD68\textsuperscript{+}/F4/80\textsuperscript{+}/CX3CR1\textsuperscript{+} macrophages.\textsuperscript{[106]} LOX (lysyl oxidase), a copper-dependent amine oxidase, maintain the ECM network by cross-linking collagen and elastin. LOX secreted from tumor cells forms the cross-links of collagen IV in the basement membranes at the pre-metastatic sites. CD11b\textsuperscript{+} myeloid cells then adhere to the cross-linked collagen IV and produce MMP-2. The collagen IV peptide cleaved by MMP-2 then enhances the further recruitment of CD11b\textsuperscript{+} cells as a chemoattractant.\textsuperscript{[107]} By increasing the extracellular activity, matrix remodeling and the creation of the pre-metastatic niche will be effective with this positive feeding loop.

Hiratsuka and colleagues established that primary tumors stimulate the expression of S100A8 and S100A9 proteins in the lung by secreting VEGF-A, TNF-\(\alpha\) and TGF-\(\beta\). The S100A8 and S100A9 proteins both generate the enrollment of macrophage antigen 1 positive myeloid cells (Mac1) into the pre-metastatic microenvironment. Neutralization of these factors with specific antibodies blocked the infiltration of Mac1\textsuperscript{+} myeloid cells and the migration of cancer cells from primary tumors to the lung.\textsuperscript{[108]} telling that the S100A8 and S100A9 proteins could play a critical role in the creation of the pre-metastatic niche. They also found that S100A8 and S100A9 induced the expression of serum amyloid A3 in alveolar macrophages as well as in endothelial cells.\textsuperscript{[109]} Broadly speaking, mononuclear phagocytes appear not only to set up preferred sites for seeding metastatic cells but also to improve extravasation of tumor cells, the formation and future growth of metastatic lesions.

8-MACROPHAGES AS ATTRACTIVE TARGETS FOR THERAPEUTIC INTERVENTION AGAINST CANCER

Evidence of many researches has demonstrated that TAM accumulation is associated with poor clinical prognosis and resistance to cancer therapy\textsuperscript{[110,111]}. However, preclinical data and sustained studies on the activity of macrophages in a solid tumor demonstrate that it significantly decreases by inhibiting CSF-1R by blocking the monoclonal antibodies. Some human monoclonal antibody in the example of RG7155 strongly inhibits the dimerization of CSF-1R. The clinical activity of RG7155 was evaluated in patients with diffuse-type giant
cell tumors and showed a marked reduction in the population of CSF-1R⁺, CD163⁺ macrophages in tumor tissues.⁹¹¹² PLX3397, a potent CSF-1R tyrosine kinase inhibitor, improved the efficacy of immunotherapy by decreasing macrophage infiltration and activating tumor-infiltrating lymphocytes.⁹¹¹³ Other studies have also demonstrated that targeting inhibition of macrophage recruitment, conversion of pro-tumorigenic M2 to antitumor M1 phenotype and suppression of TAM survival is another possible option for intra-tumor manipulation of macrophages. In spite of the fact that the reduction of the presence of macrophages associated with tumors is the main objective of these clinical studies, it should be noted that they will not all be eradicated, but rather in the sense of reprogramming them to a phenotypic anti- Tumors where they will support T-cell responses. As noted above, chemo attractants derived from the tumor and microenvironment are facilitators in the recruitment of macrophages into tumors. Thus, the inhibition of this step could become a more effective anti-cancer therapy in breast cancer animal models, the regulation of macrophages via chemotaxis is the prominent strategy to develop anti-tumorigenic therapeutic agents.⁹¹¹⁴ For example, after treatments with the receptor antagonist met-CCL5, both the number of infiltrating macrophages and the size of tumors were significantly decreased.⁹¹¹⁵ Pharmacological drugs, such as zoledronic acid combined with sorafenib, control the population of macrophages in a tumor microenvironment and enhance antitumor effects.⁹¹¹⁶ Several other pharmacological drugs are believed to block macrophage infiltration and show anti-tumoral effects, including thalidomide, linomide, pentoxifylline and genistein.⁹¹¹⁷

The conversion of macrophages of type M2 into macrophages in M1 to induce pro-inflammatory responses could be considered as the best therapeutic means. In addition, some studies have revealed that TLRs are potent candidates for enhancing the response to macrophages polarized by M1. Another recent study shows that an enzyme, SHIP1 is a crucial phosphatase that plays an important role in the conversion of the M1/M2 macrophage paradigm.⁹¹¹⁸ Moreover, the accumulated results show that macrophages are prime mediators which deliver therapeutic inducers to the environment of the tumor. Moreover, a plant-derived diterpenoid (paclitaxel) stimulates macrophages to express high levels of NO, TNF-a, and IL-1b that enhance tumor cell cytotoxicity as well as restore IL-12 production by macrophages.⁹¹¹⁹ Recently, it was reported that an anti-PD-L1 antibody, which blocks the PD-1/PD-L1 pathway, can improve macrophage-mediated T cell activation and has progressed to clinical trials.⁹¹²⁰
Fig. 1 Macrophage polarization. The macrophages will polarize into two distinct populations under the effect of several micro environmental factors (interferon, interleukin 4, 13, 10 and glucocorticoids) classically activated macrophages or M1 with an anti-tumor function and alternatively activated macrophages M2 responsible of the survival and expansion of the tumor. By the promoting the t helper cells (th1 et th2).

**Fig. 2 Summary of the function of TAMs in the tumor.**

**9-CONCLUSION**

Macrophages play an essential role from the implantation to the treatment of cancer. Their heterogeneity and plasticity induce the tumor growth, suppress local immunity or attack the
tumor cells and maintain tumor immunity. Macrophages with the support of the microenvironment polarized into substantial sub-population M1 and M2 with a dual effect pro-tumoral and anti-tumoral responsible of the presence of TAM. TAMs are usually associated with an advanced poor prognostic because of its pro-tumoral function. Overall, these finding enhance the fact that macrophages or precisely TAMs are biomarkers for a better understanding of the tumor physiology and therapy. Targeting TAMs or re-repolarization can be a good strategy in cancer therapy. Therefore, the ablation of or re-differentiation of macrophages within the tumor microenvironment will become an important tool of combination therapies designed to cure cancer. Strategies based on blocking the tumor-promoting activities of TAMs, and exploitation of macrophage anti-tumor effects or functions will allow the development of promising novel cancer treatment.

10- CONFLICT OF INTEREST
We have no conflict of interest to claim.

11- REFERENCES


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