Macrophage

Macrophages are a type of white blood cell that engulf and digest cellular debris, foreign substances, microbes, and cancer cells in a process called phagocytosis. Macrophages were first discovered by Élie Metchnikoff, a Russian bacteriologist, in 1884.

As important innate immune cells, macrophages possess the potential to engulf tumor cells and present specific tumor antigens for adaptive antitumor immunity induction, leading to growing interest in targeting macrophage phagocytosis for cancer immunotherapy.

Considered with a poor outcome of subarachnoid hemorrhage due to rupture of intracranial aneurysms (IAs), treatment interventions to prevent rupture of the lesions are mandatory for social health. As treatment option is limited to surgical manipulations, like microsurgical clipping, endovascular coiling or deployment of flow diverter, and these surgical interventions have a potential risk of complications in nature, a proper selection of rupture-prone IAs among ones incidentally found is essential. Today, a rupture risk in each case is estimated by several factors like patient characteristics and morphological ones of each lesion. However, unfortunately, an IA without treatment sometimes unexpectedly ruptures resulting in a devastating outcome or an IA surgically treated is turned out to have a thick wall. To achieve more efficient treatment interventions, the development of a novel diagnostic modality is required. Here, mainly through the accumulation of experimental findings, the crucial contribution of macrophage-mediated chronic inflammatory responses to IA progression have been revealed, making macrophage being a promising target for a diagnosis. If we could non-invasively visualize accumulation of macrophages in lesions, this imaging technique 'macrophage imaging' may enable a qualitative evaluation of IAs to stratify rupture-prone 'dangerous' lesions among many stable ones. Thereby, a development of macrophage imaging makes an indication of surgical interventions being more accurate and also greatly facilitates a development of a novel medical therapy if used as a surrogate marker [1)].

Rashad et al., from Sendai, Japan showed the intense activation of immune cells, particularly the microglia, along with the increase in macrophage activity and NLRP3 inflammasome activation that is indicated by NLRP3, Interleukin 1 beta (IL-1β), and Interleukin 18 gene and Caspase-1 upregulation and cleavage as well as pyroptosis.

Leukocytes were observed in the brain parenchyma, indicating a role in cerebral venous thrombosis (CVT)-induced inflammation. In addition, astrocytes were activated, and they induced glial scar leading to parenchymal contraction during the subacute stage and tissue loss. MMP9 was responsible primarily for the BBB breakdown after CVT and it is mainly produced by pericytes. MMP9 activation was observed before inflammatory changes, indicating that BBB breakdown is the initial driver of the pathology of CVT. These results show an inflammation driven pathophysiology of CVT that follows MMP9-mediated BBB breakdown, and identified several targets that can be targeted by pharmaceutical agents to improve the neuroinflammation that follows CVT, such as MMP9, NLRP3, and IL-1β. Some of these pharmaceutical agents are already in clinical practice or under clinical trials indicating a good potential for translating this work into patient care [2)].

Macrophages are key factors in the formation of unstable atherosclerotic plaques, which may be identified through macrophage imaging [3].

They are found in essentially all tissues where they patrol for potential pathogens by amoeboid movement. They play a critical role in non-specific defense (innate immunity), and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. In humans, dysfunctional macrophages cause severe diseases such as chronic granulomatous disease that result in frequent infections.

Beyond increasing inflammation and stimulating the immune system, macrophages also play an important anti-inflammatory role and can decrease immune reactions through the release of cytokines. Macrophages that encourage inflammation are called M1 macrophages, whereas those that decrease inflammation and encourage tissue repair are called M2 macrophages.

This difference is reflected in their metabolism, where macrophages have the unique ability to metabolize one amino acid, arginine, to either a “killer” molecule (nitric oxide) or a “repair” molecule (ornithine).

Human macrophages are about 21 micrometres (0.00083 in) in diameter and are produced by the differentiation of monocytes in tissues. They can be identified using flow cytometry or immunohistochemical staining by their specific expression of proteins such as CD14, CD40, CD11b, CD64, F4/80 (mice)/EMR1 (human), lysozyme M, MAC-1/MAC-3 and CD68.

Inflammation has been implicated in Brain arteriovenous malformation lesion progression. Among various inflammatory components, macrophage is one of the major inflammatory cells present in human ruptured and unruptured BAVM and in the BAVM lesions of animal models. The role of macrophage in BAVM pathogenesis is not fully understood. [4].

Macrophage infiltration is associated with glioblastoma Glioblastoma invasion, but the mechanisms remain unclear. Hypoxia is an outstanding characteristic of Glioblastoma tissue. Hypoxia microenvironment modulates the biological behaviors of both tumor cells and infiltrated immune cells, including macrophages.

In a study, Wang et al., analyzed the effects of hypoxia and macrophages on invasion of Glioblastoma cells and its potential mechanisms. They found that both hypoxia and macrophage supernatant promoted Glioblastoma cells invasion and matrix metalloproteinase (MMP)-9 expression, and hypoxia modulated the invasive activity of Glioblastoma cells by upregulating their CCR5 expression. The supernatant of hypoxic macrophages also showed greater pro-invasion effect than normoxic macrophages through the elevated secretion of CCL4. Moreover, they found that interferon regulatory factor-8 (IRF-8) was possibly involved in hypoxia-modulated CCL4 expression of macrophages. Taken together, the present study found that macrophages promoted Glioblastoma invasion by the CCL4-CCR5 axis, and hypoxia enhanced the interaction between these two types of cells by upregulating both CCL4 and CCR5 expression, respectively. The results of the present study suggested that hypoxia would be a potential target for the development of immune therapies of Glioblastoma [5].

Subtypes

M1 (pro-inflammatory) and M2 (reparative) macrophage.

Beyond increasing inflammation and stimulating the immune system, macrophages also play an important anti-inflammatory role and can decrease immune reactions through the release of cytokines. Macrophages that encourage inflammation are called M1 macrophages, whereas those that decrease inflammation and encourage tissue repair are called M2 macrophages.

There was a prevalence of M2 macrophage subtypes within the wall of ruptured aneurysms ($p < 0.001$). A subgroup of unruptured IAs with morphological and inflammatory changes similar to ruptured IAs was observed. The common feature of this subgroup was the presence of an intraluminal thrombus.

Conclusions: The degree of inflammatory cell infiltration associated with a shift in macrophage phenotype towards M2 macrophages could play an important role in structural changes of the aneurysm wall leading to its rupture [6].

Tumor-associated macrophage

see Tumor-associated macrophage

1)
Shimizu K, Kushamae M, Aoki T. Macrophage Imaging of Intracranial Aneurysms. Neurol Med Chir (Tokyo). 2019 Jul 15;59(7):257-263. doi: 10.2176/nmc.st.2019-0034. Epub 2019 May 11. PubMed PMID: 31080227; PubMed Central PMCID: PMC6635145.
2)
Rashad S, Niizuma K, Sato-Maeda M, Fujimura M, Mansour A, Endo H, Ikawa S, Tominaga T. Early BBB breakdown and subacute inflammasome activation and pyroptosis as a result of cerebral venous thrombosis. Brain Res. 2018 Jul 4. pii: S0006-8993(18)30362-7. doi: 10.1016/j.brainres.2018.06.029. [Epub ahead of print] PubMed PMID: 29981290.
3)
Ikeda H, Ishii A, Sano K, Chihara H, Arai D, Abekura Y, Nishi H, Ono M, Saji H, Miyamoto S. Activatable fluorescence imaging of macrophages in atherosclerotic plaques using iron oxide nanoparticles conjugated with indocyanine green. Atherosclerosis. 2018 May 18;275:1-10. doi: 10.1016/j.atherosclerosis.2018.05.028. [Epub ahead of print] PubMed PMID: 29852399.
4)
Ma L, Guo Y, Zhao YL, Su H. The Role of Macrophage in the Pathogenesis of Brain Arteriovenous Malformation. Int J Hematol Res. 2015 Jan 1;1(2):52-56. Epub 2015 Jul 6. PubMed PMID: 26495437.
5)
Wang Y, Liu T, Yang N, Xu S, Li X, Wang D. Hypoxia and macrophages promote glioblastoma invasion by the CCL4-CCR5 axis. Oncol Rep. 2016 Oct 13. doi: 10.3892/or.2016.5171. PubMed PMID: 27748906.
6)
Stratilová MH, Koblížek M, Štekláčová A, Beneš V, Sameš M, Hejčl A, Zámečník J. Increased macrophage M2/M1 ratio is associated with intracranial aneurysm rupture. Acta Neurochir (Wien). 2022 Nov 28. doi: 10.1007/s00701-022-05418-0. Epub ahead of print. PMID: 36437400.