Review Article

THE VITAL PARADOXICAL CELL-MACROPHAGES (PART – II)

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Abstract

The mononuclear phagocyte system is a complex system that can be viewed in different ways. Although tissue macrophages are anatomically distinct from one another, and have different transcriptional profiles and functional capabilities, they are all required for the maintenance of homeostasis. However, these reparative and homeostatic functions can be subverted by chronic insults, resulting in a causal association of macrophages with disease states. Understanding the precise roles of these different macrophage populations in the pathogenic response to toxicants is key to designing effective treatments for minimizing tissue damage and chronic disease and for facilitating wound repair. In this review, macrophage in metabolic homeostasis and its role in various organs have been enumerated.

Key words – Macrophages, inflammation, tissue, cytokines

Introduction

Macrophages in Metabolic Homeostasis

Macrophages are essential in maintaining homeostasis. This involves phagocytosis of debris and pathogens, dead cell clearance, and matrix turnover. Mammalian metabolic organs like liver, pancreas, and adipose tissue are composed of parenchymal and stromal cells, including macrophages, which function together to maintain metabolic homeostasis. By regulating this interaction, mammals are able make dramatic adaptations to changes in their environment and nutrient intake. For instance, during bacterial infection, innate activation of macrophages results in secretion of pro-inflammatory cytokines, such as TNFα, IL-6 and IL-1β, which collectively promote peripheral insulin resistance to decrease nutrient storage. This metabolic adaptation is absolutely necessary for mounting an effective defense against bacterial and viral pathogens because nearly all activated immune cells preferentially utilize glycolysis to fuel their functions in host defense.[1] However, this adaptive strategy of nutrient reallocation becomes maladaptive in the setting of diet-induced obesity, a state characterized by chronic low-grade macrophage-mediated inflammation.[2]

Macrophages in White Adipose Tissue

White adipose tissue (WAT) is not only the principal site for long-term storage of nutrients but also regulates systemic metabolism via release of hormones termed "adipokines". These metabolic functions of WAT are primarily performed by adipocytes with support provided by stromal cells, including macrophages. In this scenario, macrophage representation in WAT, both in terms of numbers and their activation state, reflects the metabolic health of adipocytes.[3] Although these macrophages contribute to development of insulin resistance in adipocytes, recent studies suggest that these cells also participate in remodelling of the enlarging WAT, functions that facilitate the storage of excess nutrients in adipocytes.[4]

Macrophages in Brown Adipose Tissue

For decades, it had been thought that hypothalamic sensing of cold triggers an increase in sympathetic nerve activity to stimulate the Brown Adipose Tissue (BAT) program of adaptive thermogenesis. However, recent work has demonstrated a requirement for resident macrophages in facilitating the metabolic adaptations of brown and white adipose tissues to cold. Specifically, exposure to cold temperatures results in alternative activation of BAT and WAT macrophages, which are required for induction of thermogenic genes in BAT and lipolysis of stored triglycerides in WAT.[5] Cold-induced alternative activation of BAT and WAT macrophages provides an example of how resident macrophages provide trophic support to facilitate the function of tissue parenchymal cells, in this case the white and brown adipocytes.[6]

Liver and Pancreas

Over the last few years, evidence has emerged that Kupffer cells, the resident macrophages of liver, facilitate the metabolic adaptations of hepatocytes during increased caloric intake. During obesity, an imbalance between the uptake, synthesis, and oxidation of fatty acids results in increased lipid storage in hepatocytes, a key factor in the development of hepatic insulin resistance.[7]

It has been shown that high fat feeding induces the infiltration of macrophages into the insulin-producing islets in pancreas. The increased intake of dietary lipids results in β-cell dysfunction, which induces the expression of chemokines, such as CCL2 and CCCL1 and thereby recruitment of inflammatory monocytes or macrophages into the islets. Consequently, the secretion of IL-1β and TNF-α by the infiltrating macrophages augments β-cell dysfunction, resulting in impaired insulin secretion and hyperglycemia.[8]

Macrophages in infection

When tissues are damaged following infection or injury, inflammatory monocytes are recruited from the circulation and differentiate into macrophages as they migrate into the

affected tissues. These recruited macrophages often exhibit a pro-inflammatory phenotype in the early stages of a wound healing response. If the inflammatory macrophage response is not quickly controlled, it can become pathogenic and contribute to disease progression, as is seen in many chronic inflammatory and autoimmune diseases.[9]

To counteract the tissue damaging potential of the inflammatory macrophage response, macrophages undergo apoptosis or switch into an anti-inflammatory or suppressive phenotype that dampens the pro-inflammatory response, while facilitating wound healing. These regulatory macrophages often produce ligands associated with development such as WNT ligands, which are essential for tissue repair. The mechanisms that regulate the transformation of inflammatory macrophages into an anti-inflammatory cell or suppressive macrophages and back into a proinflammatory phenotype has a major impact on the progression and resolution of many chronic diseases.[10]

Macrophages in Cancer

Tumours are abundantly populated by macrophages. Originally thought to be part of an antitumor response, clinical and experimental data indicate that in the large majority of cases macrophages promote tumour initiation, progression and metastasis. Macrophages in response to persistent infections or chronic irritation, synthesize inflammatory cytokines, IFN-γ, TNF-α, IL-6, that engage other immune cells to sustain the chronic inflammation that appears to be causal in tumour initiation and promotion . Once tumours become established, they educate the tumour associated macrophages (TAMs) away from an immunologically active state to adopt a trophic immunosuppressive phenotype that promotes tumour progression to malignancy. In established tumours TAMs stimulate tumour cell migration, invasion, intravasation as well as the angiogenic response required for tumour growth.[11] The angiogenic TAMs are characterized by the expression of the angiopoietin receptor, TIE_2, similar to that found in macrophages during development. Tumours have a proclivity to metastasize to particular sites and this phenotype is partially defined by macrophages.[12]

Macrophages in inflammatory disease

Macrophages play major roles in many chronic diseases including atherosclerosis, asthma, inflammatory bowel disease, rheumatoid arthritis, and fibrosis. In these conditions their contribution varies greatly in different situations and is controlled by many factors. For example, pulmonary macrophages produce a variety of factors that directly stimulate airway smooth muscle contractility and degradation of the ECM that contributes to pathological airway remodelling. Macrophages have also been implicated in the pathogenesis of a variety of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. In these diseases, macrophages are an important source of many of the key inflammatory cytokines that have been identified as important drivers of autoimmune inflammation. The pathogenesis of chronic demyelinating diseases of the central nervous system (CNS) has also been attributed to macrophages displaying a pro-inflammatory phenotype.[13]

Macrophages in Fibrosis

Although macrophages phagocytose and clear apoptotic cells as a part of their normal homeostatic function in tissues, when they encounter invading organisms or necrotic debris following injury, they become activated by endogenous dangers signals and PAMPs. These activated macrophages produce anti-microbial mediators like reactive oxygen species and nitrogen species and proteinases that help kill invading pathogens. However, they also produce a variety of inflammatory cytokines and chemokines that help drive inflammatory and anti-microbial responses forward, which exacerbate tissue injury and in some cases lead to aberrant wound healing and ultimately fibrosis (scarring) if the response is not adequately controlled.[14]

In contradiction, macrophages are also involved in the recovery phase of fibrosis. Macrophages act by inducing ECM degradation, phagocytosing apoptotic myofibroblasts, and by dampening the immune response that contributes to tissue injury. Therefore, current research is focused on devising therapeutics strategies that can exploit their anti-inflammatory, anti-fibrotic, and wound healing properties.[15]

Macrophages - role in dental tissues.

Large numbers of macrophages exist in the dental pulp and are considered to be the major immunocompetent cells that fight against bacterial infections caused by dental caries. However, whether dental pulp macrophages proliferate and differentiate in situ, or whether monocytes derived from the circulation differentiate into macrophages, remains uncertain.[16]

It is seen that most of the dental pulp macrophages proliferate and differentiate in the dental pulp without a supply of precursor cells from the blood stream, Macrophage –CSF might be a candidate molecule for dental pulp macrophage development, and serum factors might not directly affect the development of macrophages.[17]

In chronic periodontal infections, bacterial translocation from periodontal pockets may cause systemic release of inflammatory mediators and acute-phase proteins leading to monocyte and macrophage activation. They release cytokines, which enhance inflammation and tissue destruction.[18,19]

An important key mediator of macrophage function is the prostaglandins, which are derived from hydrolysis of membrane phospholipids. Prostaglandins have 10 sub-classes, of which D, E, F G, H, and I are the most important.[20] Inflamed oral tissues have significantly large amounts of prostaglandins. Prostaglandin E_2 is the most potent stimulator of alveolar bone resorption. Within oral lesions, prostaglandin E_2 is mainly localized within macrophage-like cells and secreted when stimulated with bacteria LPS. Periodontal ligament cells also produce

prostaglandin E_2 even at rest. This secretion is enhanced by IL-1β, TNF-α, and parathyroid hormone. Another mechanism underlying macrophage involvement in oral tissue pathologies is the destruction of ECM. Collagenases, along with other MMPs, play an important role in this process.[21]

Macrophage Tissue Expression

The use of monoclonal antibody F4/80(the 80th hybridoma in the 4th attempted fusion) led to the recognition that macrophages in tissues are very numerous, and they occupy a precise anatomical niche in relation to other tissue cell types.[22] Macrophages have a particularly intimate relationship with epithelial and endothelial cells. The ability of macrophages to extend processes across epithelia and into lymphatic vessels has also been recognized.[23]

CONCLUSION AND FUTURE PERSPECTIVES

Macrophages are involved in almost every disease and represent attractive therapeutic targets because their function can be augmented or inhibited to alter disease outcome. Therapeutic targeting of macrophages is now well underway. Most of the therapies are targeted at pan-macrophage markers such as the CSF1R. Strategies in fibrosis and cancer have been to target recruitment of macrophages particularly through inhibition of inflammatory monocyte trafficking. In other circumstances, the protective effects of recombinant human serum amyloid P (SAP also known as pentraxin-2) in Idiopathic Pulmonary Fibrosis and post-surgical scarring in patients treated for glaucoma is thought to be through the reduction of inflammation and fibrosis by inducing the production of IL-10 in regulatory macrophages. Neutralization of GM-CSF using antibodies is being tested in phase II trials for multiple sclerosis and Rheumatoid arthritis. In the future it seems it will be possible to exploit the inherent plasticity of macrophages to adjust their set points to control obesity by down-modulating inflammatory cytokines, to resolve fibrosis by inducing the differentiation of resolving macrophages and to treat cancer by converting macrophages from their trophic to an immunologically activated anti-tumoral state.

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