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Review

Alveolar macrophages in diabetes: friends or foes?

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ABSTRACT

AMs constitute an important bridge between innate and adaptive immunity. AMs patrol the lungs against pathogens, remove senescent cells, and help repair tissue. AM function is altered in many diseases, including DM, where AM abnormal immune responses may worsen infections or lead to exacerbation of inflammatory reactions. In vivo experimental models have greatly contributed to our knowledge of AM function. Studies have shown that during hyperglycemic states, the phagocytic function of AMs and the expression of adhesion molecules may be altered, interfering with the recruitment of immune cells to the inflammatory site. Insulin treatment seems to recover the normal function of impaired AMs. However, much research is still needed to characterize AMs and to better understand their role in inflammation and infection, particularly in diabetic patients. In this review, we attempt to explore recently accumulated knowledge about AM function and how this function is deficient in DM. Additionally, AM polarization is compared briefly with that of T cells, and this may interfere with how immune response is driven. This review discusses how impaired AMs lead to an aberrant immune response that contributes to worsening infection and autoimmunity, opening up discussion for future work in the field. *J. Leukoc. Biol.* 91: 871–876; 2012.

Introduction

Macrophage patrolling protects the body against invaders and foreign bodies. Since the first description in phylogenetic studies in 1892, various tissue-specific functions have been attributed to macrophages [1]. They are believed to carry out important functions, such as phagocytosis, antigen processing, and presentation, which are key mechanisms by the interaction between the innate and adaptive immune systems.

Using their PRRs, AMs are able to recognize molecules carrying repetitive, patterned moieties. This recognition is fundamental for initiating an immune response against mammal-infecting pathogens. Following phagocytosis, the pathogen is degraded within the macrophages. Next, it may be presented on the cell surface, usually via the MHC II. During antigen processing and presentation, cytokines are released with the main purpose of recruiting to the inflammatory site other immune cells, such as neutrophils, DCs, NK cells, and lymphocytes.

In many diseases, the inflammatory response can be abnormal. In AIDS, for example, the patient may not be able to build an appropriate immune response because of the destruction of circulating lymphocytes [2, 3]. In systemic lupus erythematosus, organs may be targeted by autoreactive antibodies [4] as a result of an abnormal immune response. In DM, many functions in immune cells are deficient, possibly leading to recurrent infections in patients who maintain a chronic hyperglycemic state. Pulmonary infections may lead to septicemia, which requires intensive care treatment and in most cases, is fatal. Our review focuses on recent knowledge regarding AMs and possible molecular pathways in DM that can contribute to a failure of AM responsiveness to infection.

AMs: IMPORTANCE, ORIGIN, AND FUNCTION

AMs are important for the maintenance of lung homeostasis. Specifically, they are responsible for the clearance of senescent cells and also contribute to tissue repair after infection or tissue injury. As the human respiratory tract is in constant contact with pathogens, host-defensive strategies, such as coughing, cilia movement, and mucus lining the bronchi and bronchioles, are required to trap the pathogen and to prevent it from reaching the alveoli. If the pathogen does reach the alveoli, it can easily circulate in the body through pulmonary capillaries. Thus, AMs in the alveoli represent a vital defense mechanism for the host [5].

Studies have shown that AMs derive from bone marrow [6], but little is known about them. A clear distinction has still not been made between mononuclear cells that enter the lungs

Abbreviations: AM=alveolar macrophage, BALF=BAL fluid, DM=diabetes mellitus, TAM=tumor-associated macrophage, U-PM=urban particulate matter

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during an infection to become AMs and AMs that differentiate from pulmonary resident monocytes. Moreover, the stimulus for macrophage migration to the lungs and the stimuli driving AM differentiation are still unknown. An additional question regarding AMs is whether differentiated AMs retain any plasticity. Answers to these questions could help the physician toward better treatment and promote faster healing of lung infection or injury.

Many conditions can lead to altered macrophage function. In lung cancer, AMs show impaired phagocytosis [7], but the cytokine profile and the adhesion molecule expression seem to vary according to histological characteristics of the tumor. Levels of secreted TNF-α and IL-1 from AMs of patients with small, squamous, or large cell undifferentiated carcinoma are lower when compared with those of the controls [7]. Conversely, AMs from adenocarcinoma patients show similar levels of IL-10, IL-6, IL-1, and TNF-α when compared with those of the controls [7]. In cancer, monocytes from blood circulation can also be recruited to the tumor site and may represent ~50% of the tumor mass [8]. Macrophages that infiltrate the tumor are called TAMs, and their antitumor function in lung cancer has not yet been elucidated [9]. When present at high levels, these infiltrating macrophages are associated with poor prognosis [8]; as such, they can induce tumor angiogenesis and metastasis [10]. Animal models have also suggested that conditions of modern life can contribute to the configuration of macrophages. For example, AMs, exposed in vitro to U-PM SRM1648, showed dose-dependent cytotoxic effects [11].

MACROPHAGES AND THEIR POLARIZATION

As with T cell differentiation, macrophages can polarize into classical (M1) or alternative (M2) types. Experimental animal models have shown that a stimulus is essential to determine which pathway macrophages should follow. Generally, M1 cells tend to develop under an IFN-γ microenvironment and are capable of inducing resistance to viral or intracellular bacterial infection, as well as to cancerous cells [12]. They produce more reactive oxygen and nitrogen intermediates [13] than M2 macrophages, and they present IL-12^{high}, IL-23^{high}, and IL-10^{low} phenotypes. An acute pancreatitis-associated lung injury model suggests that AMs associated with classical [14] differentiation can also increase in number, 24 h after induction, can express inflammatory cytokines, and can activate NF-κB.

Conversely, M2 cells seem to depend on an IL-4 or IL-13 environment and on other transcription factors, such as STAT-6 and peroxisome proliferator-activated receptor-γ [15]. Moreover, they show high expression of arginase 1, mannose receptor 1, or CD206 [15], anti-inflammatory cytokine IL-1R antagonist, and IL-10 [16]. It has also been suggested that PI3K activation and SHIP, a PI3K-negative regulator, are requirements for M2 skewing [13].

Plasticity is another important feature of mononuclear phagocytes. In an experimental arthritis mouse model, for instance, liposomal glucocorticoid treatment is likely to inhibit M1 differentiation toward M2 polarization [17], causing mononuclear phagocytes to acquire a more regulatory phenotype. This capability of configuring and reprogramming themselves in response to a stimulus is a unique characteristic of phagocytes. Even though a precise characterization of macrophages does not seem plausible, efforts should be made toward a better understanding of what functions they are capable of exerting and how they can modulate the host immune response. Therefore, we list in **Table 1** some of the markers that we believe are expressed on AMs.

TAMs are still under thorough investigation. Although it seems reasonable to think that TAMs would differentiate ac-

TABLE 1. AMs: Receptors and Phenotype

Macrophage receptor	Function
F4/80^{low}–CD11b	F4/80: murine—pan macrophage marker—biological ligand for F4/80 has not been identified, but it is believed that F4/80 is required for induction of CD8 T cell-mediated peripheral tolerance [18] CD11b: human—inflammation marker on macrophages, complement receptor [19, 20]
CD68	Scavenger receptor that binds to LDL [21, 22]
Dectin-1/CD63	Murine and human, respectively: in cooperation with TLR2, induces proinflammatory cytokines [23]
Sialoadhesin (Siglecs)	Binds to sialic acid ligands, expressed on resident and inflammatory macrophages [24]
Mannose receptor (CD206)	Binds to mannose, fucose, and endogenous glycoproteins [23]
Tissue factor	Seems to be directly related to macrophage maturation; initiates the extrinsic coagulation pathway [25]
Scavenger receptor (collagenous)	Important nonopsonic receptor for modified LDL, acetylated LDL, and other polyanions, including lipid A; possible role in atherogenesis [23]
CD69	Activation marker after microbial stimuli; physiological ligands are unknown [23, 26]
CD14	Receptor for LPS, recognition of apoptotic cells [27]
Phosphatidyl serinereceptor	Binds to ICAM-3 on the surface of apoptotic cells [28]
Scavenger receptor (noncollagenous) CD36	Phagocytic marker [28]

cording to the IFN-γ microenvironment, they present a M2 phenotype [29]. There is some evidence that macrophages co-cultured with tumor cells can release substances that stimulate tumor growth [8]. TAMs produce CCL2, a chemokine that acts by recruiting monocytes and that is related to autoimmune pathogenesis [30].

AMs IN DIABETES: WHICH GOD DO THEY FOLLOW?

DM is a metabolic state in which insulin is not produced in sufficient amounts, or insulin function is altered, causing a hyperglycemic state. Since 1923, when a Nobel Prize was awarded to Bantin and Macleod, there has been strong evidence that insulin is more than a polypeptide that regulates glucose uptake by cells and prevents or controls the onset of DM [31–33]. Insulin can act as an immunomodulatory compound, as well as a facilitator of the coagulation cascade, and it may also attenuate catabolic states [34]. Studies have found that microvascular and neurologic dysfunctions are common complications associated with DM and that their severity might be correlated directly with the duration of the hyperglycemic state [35]. A wide range of immune cell function is also deficient in diabetic patients [36, 37]. From chemotaxis and adherence to intracellular destruction of pathogens, many processes that are normally performed by leukocytes and that are vital to the normal clearance of a "microinvader" are impaired in the absence of insulin [34–37].

Studies have also demonstrated that phagocytic abilities against fungi are weakened in polymorphonuclear cells (neutrophils) of diabetic rats [38]. Phagocytosis is also impaired in AMs and restored after insulin administration [39]. Moreover, some adhesion molecules, such as ICAM-1, and the production of proinflammatory cytokines, such as TNF-α, seem to be impaired in neutrophils from the BALF of diabetic rats [40–43]. Using diabetic Wistar rats, another study has suggested that asthmatic diabetic animals show altered concentrations of IL-1β and TNF-α in BALF, along with altered platelet-selectin expression on lung microvessels when compared with controls [44]. In addition, U-PM exposure seems to affect AM function in diabetic rabbits [11]. In this particular study, diabetic AMs are suggested to generate more ROS and to have higher levels of cytokine expression compared with normal AMs.

There is additional evidence indicating that DM can change TLR expression. Monocytes purified from the peripheral blood of diabetic patients show increased of expression of TLR2 and -4 compared with controls [45]. In a mouse experimental model, the hyperglycemic state also changes TLR expression in bone marrow-derived macrophages [46]. There is a lot of controversy regarding TLR expression in diabetic cells [45–48]. In diabetic lungs, however, the exact mechanisms underlying AM and pathogen recognition through TLRs remain unclear.

Although macrophages can have their functions changed according to the situation, the mechanisms behind these changes need to be elucidated. In an experiment with human AMs, from smoker and nonsmoker volunteers, results suggested that TLR expression of AMs from smokers is slightly lower than that from nonsmokers, although no significant difference regarding cytotoxic activity in smokers was detected when stimulated with LPS [47]. This result was based on superanion production capacity and tumoricidal activity in smokers, but the mechanism underlying the enhancement of proinflammatory activity in smokers and recruitment of immune cells to the site was not elucidated. LPS is also present in various bacterial cell walls. As such, infection with *Pseudomonas aeruginosa* provokes severe complication in patients in intensive care units and seems to trigger TLR4 recognition in murine AMs [48] through the MyD88 pathway. It has also been suggested that two ligand/receptor pairs are needed to trigger the MyD88 pathway.

In asthma, an important immune-mediated inflammation [44, 49, 50], it has been suggested that the pathway that ameliorates the crisis in experimental models through the transferring of AMs resembles the GM-CSF-dependent pathway [50]. These results need to be investigated further. Conversely, diabetic patients seem to be protected from acute lung injury/acute respiratory distress syndrome, but the mechanisms underlying this decreased risk are not well understood [34].

How other hormones may affect AMs is still unclear. In vivo studies have been performed in animal models with insulin and in others lacking insulin, as well as in animal models having corticosteroids and in others lacking them. Corticosteroids seem to cause an imbalance that leads to oxidative stress and consequently, results in a dose-dependent inhibition of TNF-α and IL-8 secretion by a human monocytic cell line, which could be a problem when treating patients, as those with pulmonary infections are commonly treated with antibiotics and dexamethasone [51]. Insulin, on the other hand, seems to protect the patient against an over-reactive inflammation, which might be more destructive to the tissue than contributing to clear infection.

In fact, insulin is an anabolic hormone, which like glucagon, is fundamental for regulating blood and tissue glucose levels. Considering that the brain metabolism seems to be insulin-independent, one wonders how cerebral glucose is controlled [52]. It would be of great relevance to understand this "insulin-free milieu", as this microenvironment is highly dependent on the presence of glucose and is not vulnerable to blood insulin oscillations [52] or to a lack of insulin, as occurs in DM1.

In chronic diseases, such as DM, it is important to find biomarkers, which indicate the disease state and can be used for patient prognosis. Moreover, it is essential to understand which cells and functions are defective at each state. It is important to point out that infection is not an invariant state and that the infectious agent can also drive the way the organism responds to the aggression. Suppose that a diabetic patient is infected with *Mycobacterium tuberculosis*, a highly subversive intracellular bacterium that can manipulate the host immune system to act on its behalf. Almost 10% of the infected patients keeps the bacilli in a latent state and does not develop active tuberculosis. Some strains are highly resistant to nitrogen intermediates, protecting them from being degraded by the host immune system. Others are capable of interfering with the machinery involved with phagolysosome tethering and fusion [53]. Considering that the diabetic patient already

has a phagocytic deficiency, how does this patient deal with tuberculosis? Would a phagocytic incapacity be enough to promote sepsis, or would the phagocytic inability allow the bacteria to spread and to have "metastatic" foci in other organs, leading to renal or genitourinary tuberculosis?

As a facultative intracellular organism, *M. tuberculosis* might survive for some time, circulating in the peripheral blood. When entering the lungs, it can be recognized by AMs and by other innate immune cells through TLR2, which can recognize peptidoglycan displayed on bacilli walls. If the expression of TLR2 is altered [46] in DM1 cells, how does this benefit the patient? The molecular mechanisms underlying the relationship between DM1 and TLR expression in the lungs have not been clarified, but we predict a role for IFN-γ in this relationship. IFN-γ is known to be up-regulated in intracellular infection [54] and to increase MHC II expression in macrophages.

The well-known association between DM and tuberculosis is alarming. Many studies have reported that DM negatively affects tuberculosis control. Thus, in endemic areas of tuberculosis, different strategies should be adopted for better control of DM. It has been proposed that active searching for DM cases may help detect latent cases of tuberculosis and that treatment of these patients may have a positive impact on tuberculosis control [55]. In India, DM is an aggravating factor for infectious tuberculosis [56], especially in urban areas. Thus, DM treatment is important for blocking tuberculosis dissemination in endemic areas.

DM is believed to be a TH1 cell-mediated disease [57]. Diabetogenic macrophages are supposed to help with the "priming of pathogenic T cells", which infiltrate the pancreas [57]. It is suggested that *M. tuberculosis* inhibits IFN-γ up-regulation, leading to reduced priming of naïve T cells. A 15-month follow-up of diabetic patients showed that IFN-γ-producing cells are deficient in diabetic patients. Authors of the study suggested that these deficient cells may travel to the pancreas and that years later, they make the β cells highly susceptible to viral infections [58]. In the lungs, however, it is not known how this altered priming interferes with cell recruitment and cytokine release. The association between DM and tuberculosis may be explained partially by an IFN-γ deficiency, but whether these defective T cells can influence AMs is uncertain. Although insulin treatment can recover adhesion molecule expression, phagocytic cell recruitment, and the production of IFN-γ, whether or not the function of AMs is restored, remains unclear. Furthermore, the lack of IFN-γ-producing cells in the lungs can lead to inefficient AM activity, which may explain the failure of the innate and adaptive immune responses, transforming the pulmonary infection into septicemia or even leading to the appearance of autoimmune diseases. Many hypotheses might be constructed regarding diabetic AMs and related infection control failures. What we have tried to describe here is the relationship among TLR expression, failure to destroy pathogens, and the burden of an autoimmune disease or even septicemia (**Fig. 1**).

FINAL REMARKS

It has been shown recently that autophagy is associated with DM pathogenesis. As such, this pathway modification can explain hyperglycemic states and insulin deficiency [59]. The autophagy pathway is associated with β cell apoptosis and decreased proliferation, which lead to a reduced mass of pancreatic β cells. Imbalanced cytokine production and distorted cell signaling may promote altered gene expression and regulation in AMs. In addition, the fact that lymphocytes are incapable of releasing the proper number of immune modulators or are unable to prime the proper cells might create a continual loop of deficient immunity, which may result in sepsis or cancer. Finally, the function of AMs in patients with lung infec-

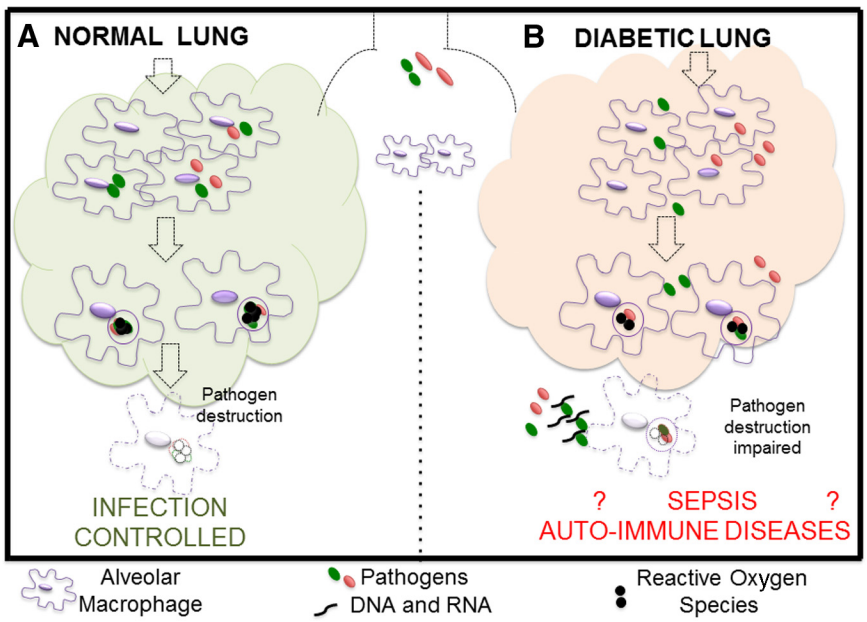

Figure 1. AMs and lung infection. (A) AMs, in normal circumstances, are able to phagocyte pathogens and clear the infection. (B) In diabetic patients, AMs fail to control infection as a result of many factors, such as phagocytic impairment, cytokine profile changes, and ROS activity failure. In this case, pathogens inside macrophages are unlikely to be processed entirely, and either burden of pathogens might incur in sepsis or autoimmune diseases.

tions is impaired, resulting in an ineffective inflammatory process and aberrant communication between innate and adaptive immunity. The role of AMs needs to be considered in the search for an effective treatment for lung infection. Moreover, AMs should be seen as paramount to the immune response in DM patients.

In conclusion, AMs are a key factor in the maintenance of lung homeostasis. Although it is not possible to say that AMs are solely responsible for the unsuccessful control of lung infection, they most likely worsen an existing infection. It is possible that "foe" AMs in diabetic patients are configured to become "friendly", although the molecular mechanism underlying this potential phenomenon still needs to be elucidated.

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