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Critical review

Molecular

Alveolar macrophages and pulmonary surfactant—more than just friendly neighbours

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Abstract

Introduction

Located at the alveolar surface of the lung, both alveolar macrophages and pulmonary surfactant play an important role in innate host immunity whereby they protect the lung from various inhaled particles, chemicals and infectious agents. While alveolar macrophages are complex cells that exhibit both pro- and anti-inflammatory functions that are origin and circumstance-dependent, surfactant is a relatively consistent and stable material composed of phospholipids and proteins. Nevertheless, as will be outlined in this brief review, these two components exhibit marked interaction and interdependence in both undisturbed and activated conditions. Furthermore, disruption of this relationship between alveolar macrophages and surfactant may be a contributing factor to various lung conditions such as the acute respiratory distress syndrome.

Conclusion

Abundant literature exists to support a dynamic interaction between alveolar macrophages and pulmonary surfactant in both undisturbed and diseased states. This relationship may have important implications for the management and treatment of various pulmonary diseases.

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Introduction

Alveolar macrophages (AMs) represent a critical component of the host innate immune system that, under basal conditions, have been shown to play a role in the pathogenesis of several pulmonary diseases[1]. Unlike tissue macrophages found in other organs, AMs are placed in an anatomic position where there is perpetual exposure to the external environment on a 'breath-by-breath' basis. As such, the AMs serve as the first line of defence against any inhaled material including environmental pollutants, infectious agents (viruses, bacteria, etc.) and ambient air. The need for AMs to respond efficiently to a broad range of insults places a high burden of responsibility on these cells to recognise and respond appropriately to ensure that suitable pro-inflammatory and anti-inflammatory mechanisms are invoked, thereby allowing normal lung homeostasis to be maintained on a long-term basis.

Similar to AMs, pulmonary surfactant is also continuously exposed to the external environment based on its anatomic positioning. It is a mixture of lipids and proteins that line the alveolar surface, and represents the initial interface encountered by inhaled particles that reach the alveolus[2]. In addition to its more well-known functions in providing alveolar stability and facilitating blood oxygenation[2], several lines of evidence support a crucial role for surfactant in protecting the lung through a number of innate host defence mechanisms[3–5]. Thus, based on the shared environment of the AM and surfactant within the distal airspaces of the lung, it is not surprising that complex interactions exist between these two components of the distal airspaces.

Overall, there is abundant evidence to support the notion that resident AMs are critically involved in the alveolar metabolism of surfactant, which will be outlined below. Conversely, there is also ample experimental data demonstrating that surfactant, and its individual components strongly influence the behaviour of AMs. Over the past several years, a more detailed description of specific AM function has emerged that has further enhanced our understanding of the interactions between AMs and pulmonary surfactant including: (i) the distinction between resident and recruited alveolar macrophages and (ii) the description of a novel concept referred to as 'macrophage polarisation'. The following review will highlight the current state of this knowledge on the dynamic interactions between the AM and pulmonary surfactant and their potential implications to enhance our understanding of disease specific processes.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was also in accordance with the institution guidelines.

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Surfactant-dependent alterations in alveolar macrophage phenotype

Under basal conditions, the macrophage population within the lung consists almost exclusively of well-differentiated resident AMs that can be identified by specific phenotypic surface markers such as CD11c and DEC-205, in contrast to the majority of non-resident AM populations that express CD11b. Despite years of research, the origin, half-life and functional characteristics of resident AMs continue to be an area of active investigation. It has been shown that local factors within the alveolar environment provide a potent stimulus for recruited circulating bone marrow-derived monocytes to develop specific resident AM characteristics[6]. Although variation has been reported, the half-life of AMs appears to be remarkably long compared with macrophage half-life found in other locations[7]. For example, Murphy and colleagues[7] demonstrated in murine lungs that there was negligible AM turnover over an eight-month period, suggesting that the bone marrow-derived circulating monocytes do not contribute actively to AM renewal under steady state conditions. Although this turnover may be slow, other studies have suggested that the replacement rate of resident alveolar macrophages by peripheral monocytes occurs at a rate of approximately 40% annually[8]. As an alternate mechanism by which circulating monocytes lead to the AM lineage, Landsman and Jung[9] suggested that alveolar macrophages may be, in part, derived from an intermediate macrophage that resides in the alveolar interstitium, which is capable of expanding the population of cells within the alveolar space. Nonetheless, these studies provide compelling evidence of a prolonged life span of the resident AMs.

The surfactant system plays an intricate role in a number of the aforementioned processes that lead to the unique AM phenotype (Figure 1). In this regard, the most widely studied components include the surfactant-associated proteins A (SP-A) and D (SP-D)[4]. Evidence supporting an effect of SP-A on AM phenotype was reported by Phelps and colleagues, who examined the AM proteome from SP-A knockout (KO) animals, wild-type mice and mice treated with exogenous SP-A[10]. They identified functional changes in KO AM compared with wild-type in proteins associated with cell motility, phagocytosis and oxidative stress. A majority of these changes were restored towards the

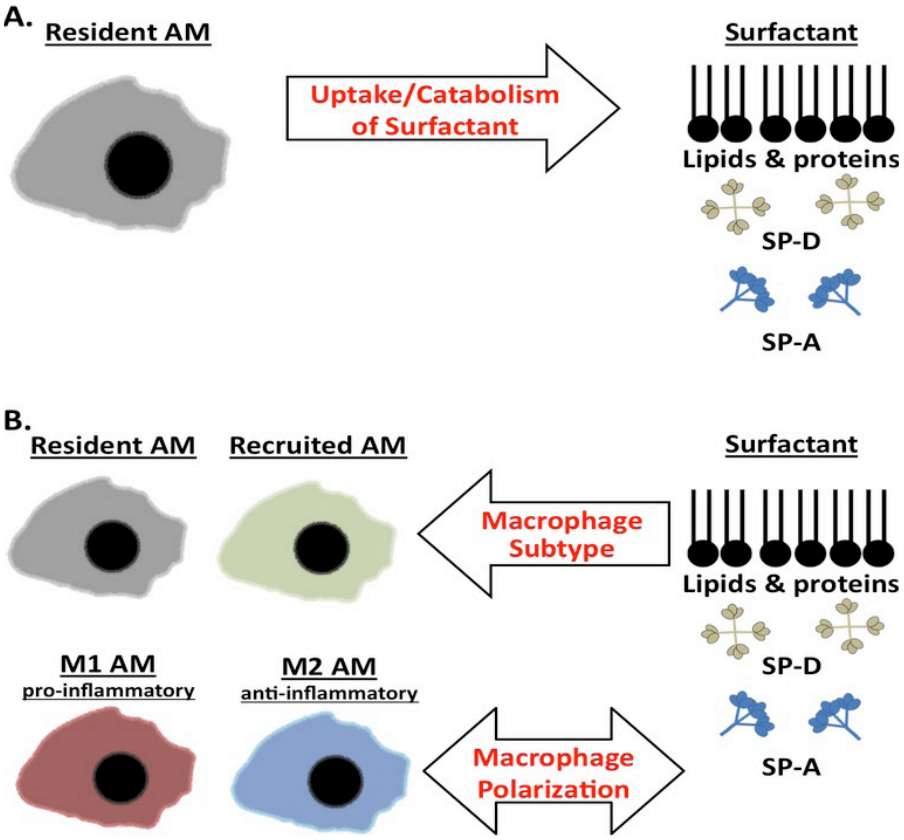

Figure 1: Mechanisms of interaction between alveolar macrophages (AM) and pulmonary surfactant within the alveolar airspaces. AM and pulmonary surfactant play an important role in innate host immunity, protect the lung from various inhaled particles, chemicals and infectious agents, and exhibit marked interaction and interdependence in both healthy and injured/infected lungs. (a) The resident AM is a key contributor to ongoing turnover of surfactant components from the airspace in both mice and humans. Impaired AM surfactant catabolism, which is observed in animal models of AM depletion or in patients with pulmonary alveolar proteinosis, leads to a marked increase in surfactant pool sizes. (b) Surfactant, specifically the surfactant proteins (SP-A and -D), affects AM functions such as cell migration, phagocytosis of pathogens and apoptotic cells, and polarisation. Surfactant proteins promote phagocytosis by macrophages and in certain models of injury, promote M1-polarisation of macrophages. Conversely, cytokines from M1-polarised macrophages have been shown to decrease the expression of surfactant proteins within the lung following infection.

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wild-type phenotype in AM obtained from KO animals receiving intra-tracheal exogenous SP-A administration. Similarly, a role for SP-D in the development of an AM phenotype has also been suggested based on studies performed in SP-D deficient animals. For example, Levine and colleagues demonstrated altered integrin expression of AM from SP-D KO animals[11], and furthermore, Yoshida and Whitsett[12] reported altered NF-κB activation and matrix metalloproteinase production of AM obtained from KO animals, as compared with wild-type animals. In addition, Guth et al.[6] utilised cell transfer techniques to demonstrate that the environmental conditions within the lung contribute to the AM phenotype and suggested, based on *in vitro* observations, that SP-D increases CD11c expression of bone marrow-derived cells. Together, these studies support a key role of surfactant in the modification of AM function.

The contribution of alveolar macrophage towards surfactant metabolism

In addition to the phagocytic and innate immune properties of AM within the airspaces, strong evidence exists to support a key role of resident AM in maintaining alveolar surfactant homeostasis. In the healthy lung, pulmonary surfactant pool sizes and function are maintained through processes that include synthesis, secretion, reuptake, recycling and catabolism. The alveolar type II cell represents the primary cell type involved in all metabolic functions; however, abundant evidence exists to support a role of the resident AM in contributing to ongoing removal of surfactant components from the airspace[13–15]. A metabolic study by Rider and colleagues[16] utilised degradation-resistant lipid analogues to demonstrate that the AM was responsible for approximately 20% of surfactant clearance. Subsequently, the importance of this catabolic activity was highlighted based on the observed phenotype of the granulocyte macrophage colony-stimulating factor (GM-CSF) null mice[17,18], which exhibit a marked increase in surfactant pool size similar to that observed in the human condition of pulmonary alveolar proteinosis. A series of elegant studies determined that absence of surfactant catabolism by AM was the primary factor leading to the observed increased surfactant pool sizes[17,19]. Parallel studies in the human pulmonary alveolar proteinosis patients identified anti-GM-CSF autoantibodies as an underlying feature in a large number of patients affected by this condition[20]. Further evidence utilising an intra-tracheal instillation of dichloro-methylene-diphosphonate (DMDP) encapsulated liposomes in rats that depletes the AM population by approximately 70% to 80% resulted in a nine-fold increase of pulmonary surfactant pools within seven days[21]. Collectively, this data demonstrate the importance of AM in maintaining normal surfactant pool sizes.

Surfactant and recruited macrophages

Under basal conditions the AM population is relatively stable; however, macrophage numbers within the airspaces have the propensity to increase significantly under conditions of significant stress. Generally, the robust increase in macrophage number has been shown to occur through the recruitment of circulating peripheral monocytes, which subsequently differentiate into macrophages, within the alveolar spaces. Such infiltration of macrophages leads to distinct macrophage populations within the alveolar space, each with specific roles during acute inflammatory response and resolution of lung injury. For example, Janssen and colleagues[22] demonstrated that recruited circulating macrophages represent the predominant macrophage lineage within the airspace after intra-tracheal LPS stimulation. During the resolution phases of inflammation, these recruited macrophages undergo local apoptotic clearance marked by high level expression of the surface bound death receptor, Fas. Similarly, Maus and colleagues[8] utilised CD45.2 bone marrow chimeras to show that although alveolar macrophage turnover is slow under basal conditions, a brisk increase in turnover and replacement of AM occurs after intra-tracheal LPS administration. Studies such as this suggest that in the setting of acute inflammatory responses, resident AM and recruited macrophages represent distinct populations within the airspaces and may play independent roles in both the acute and resolving phases of injury.

Although the potential involvement of surfactant in these processes is widespread, only limited studies have been published that address the differential effects of surfactant on 'resident' versus 'recruited' AM (Figure 1). Both *in vitro* and *in vivo* studies have demonstrated that SP-A and SP-D act as opsonins and thereby enhance phagocytosis of inhaled pathogens[23]. These surfactant proteins have also been demonstrated to modulate the release of inflammatory mediators by AM, thereby impacting innate inflammatory responses within the lung. A particularly interesting finding with regard to the resolution of injury is evidence that SP-D binds apoptotic cells and enhances the clearance of these by AM[24]. This broad array of activities of SP-A and SP-D is matched by a wide array of receptors and signalling pathways associated with these processes, which is beyond the focus of the current review. In addition, studies with macrophages derived from peripheral blood monocytes have demonstrated that even the surfactant lipids can impact the behaviour and phenotype of macrophages[25].

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Surfactant and macrophage polarisation

A second concept that highlights the broadness and complexity of AM function is macrophage polarisation. It has been clearly demonstrated that macrophages are capable of responding to a variety of stimuli, and depending on the specific stimulus, are able to promote or inhibit inflammation; this divergent response by the macrophage has been termed macrophage polarisation. Initial studies classified macrophages into two groups: M1 and M2 polarised macrophages[26,27]. Subsequently, M2 macrophages were further subclassified into M2a, M2b and M2c macrophages, and another subtype, the regulatory macrophage, was also identified[26].

The M1 macrophage is induced by pro-inflammatory T helper 1 (T_H1) cytokines, such as interferon (IFN) γ, or by bacterial byproducts, such as lipopolysaccharide (LPS)[26,28]. M1 polarisation is characterised by the production of pro-inflammatory factors like interleukin (IL) 6, inducible nitric oxide synthase (iNOS), tumour necrosis factor (TNF) α and monocyte chemoattractant protein (MCP) 1/CCL2[26,28]. Ongoing M1 polarisation, leading to excessive inflammation, is thought to result in increased tissue damage[29]. In general, the M2 phenotype, which is induced by the T_H2 cytokines IL4 and IL13, but which can also be driven by immune complexes and IL10, is characterised by production of anti-inflammatory molecules like IL10 and transforming growth factor (TGF) β1[26,28]. While M2 polarisation is associated with the resolution of inflammation, M2 polarised macrophages, specifically M2a polarised macrophages, can also activate myofibroblasts leading to enhanced fibrosis[29]. In contrast, the regulatory macrophage is thought to promote the resolution of fibrosis following injury[29].

The concept of macrophage polarisation is further complicated by the fact that macrophages from different tissues or compartments (e.g. recruited versus resident macrophages) appear to vary in their polarisation response to similar stimuli. Some *in vitro* studies have suggested the resident AM is hyporesponsive to inflammatory stim-uli, such as LPS, and as a result, expresses lower levels of genes associated with M1 polarisation[30]. Examination of macrophage polarisation *in vivo* following *Pseudomonas aeruginosa* infection, however, demonstrated that the resident AMs become strongly M1 polarised[31]. Interestingly, macrophages recruited to the lung following *P. aeruginosa* infection were initially M1 polarised, but later became M2 polarised, suggesting that recruited macrophages are capable of both promoting and inhibiting inflammation, whereas the resident macrophages are predominantly pro-inflammatory[31].

The influence of surfactant on macrophage polarisation has not been studied in great detail; however, the evidence described above for the impact of surfactant on macrophage behaviour in general, implies a potentially significant impact of surfactant on macrophage polarisation. Existing evidence stems from a study by Mitsuhashi and colleagues[32], which indicates that SP-A could directly affect the polarisation of lung tumour-associated macrophages (TAMs). Specifically, overexpression of SP-A by lung adenocarcinoma cells used in mouse lung metastasis studies led to a significant increase in the number of M1-polarised TAMs, ultimately leading to increased natural killer cell recruitment and decreased lung tumour progression[32]. Thus the interaction of surfactant and macrophages may affect polarisation (Figure 1). Furthermore, a recent study by Bein and co-workers[33] demonstrates that cytokines from M1-polarised macrophages, specifically TNFα, repress SP-B (*Sftpb*) expression by pulmonary epithelial cells. SP-B is decreased (both mRNA and protein) in mouse models of pneumonia. Stimulation of pulmonary epithelial cells with LPS *in vitro* had no effect on *Sftpb* expression, whereas treatment with conditioned medium from LPS-stimulated (M1) macrophages decreased *Sftpb* promoter activity and expression[33]. This provides at least preliminary data of an effect of polarisation on surfactant composition and suggests that the impact of AM polarisation on surfactant metabolism should be further investigated.

Surfactant and alveolar macrophage interactions—Implications for lung disease

The AMs and pulmonary surfactant are not only crucial to the maintenance of lung homeostasis under basal conditions but there is also intimate relationship within the alveolar space that may place this interaction at the centre of a variety of lung pathologies. A prototypic disease in which AM-surfactant interaction is disturbed can be observed in the setting of pulmonary alveolar proteinosis, in which an impairment of surfactant uptake by AM leads to the accumulation of surfactant in the lung. By and large, the mechanisms involved in this process, including the role of anti-GM-CSF auto-antibodies, have been well established in both animal and clinical studies[17]. In a majority of other disease processes, changes in surfactant composition and function, and altered immune modulatory functions of AMs have traditionally been described independently (e.g. invasive pulmonary infections, cystic fibrosis and idiopathic pulmonary fibrosis)[34]. Overall, evidence to support a specific cause-and-effect relationship between altered AM function and impaired surfactant in these clinical situations is limited to few isolated animal studies.

One specific clinical condition in which AM-surfactant interaction may play a central role in disease

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pathophysiology is in the setting of the acute respiratory distress syndrome (ARDS)[23]. ARDS is defined primarily by the physiological criteria of impaired gas exchange and is characterised by leakage of protein rich oedema fluid into alveolar spaces, coupled with an intense local inflammatory response. Previous studies have employed intra-tracheal instillation of clodronate/DMDP liposomes to specifically deplete the resident AM population in the lung prior to injury. In these studies, reduction in macrophages during ventilator-, hyperoxia-, or endotoxin-induced lung injury often leads to less severe inflammation thereby suggesting that resident AMs are key propagators of the inflammatory response[35–38].

Parallel to these findings are numerous studies on the alterations of surfactant in the setting of ARDS. Characterisation of the composition and function of surfactant both in patients with ARDS and in animal models of the disease have demonstrated altered lipid composition, decreased surfactant proteins and impaired function associated with this syndrome[39–41]. The functional impairment of surfactant may directly contribute to physiological lung dysfunction, whereas compositional alterations in surfactant may also contribute to altered inflammatory responses. Collectively, these studies suggest that AM and surfactant are key contributors to the development and resolution of lung inflammation. Evidence that direct AM–surfactant interactions may play a role in these processes has been shown in *in vitro* studies in which SP-A or SP-D was administered to stimulated AM *in vitro*; in general, co-administration of surfactant results in a down-regulation of the AM inflammatory response. Studies evaluating the effect of macrophages on surfactant pool sizes in the setting of ARDS have also been limited. Using radiolabelled tracers of surfactant, it has been shown that macrophages obtained from rats with sepsis-induced ARDS had an enhanced uptake of surfactant[42]. Overall, the observations to date provide strong rationale for potential macrophage–surfactant interaction at the core of the pathophysiological processes of ARDS; however, *in vivo* studies are limited and further research is required.

Conclusion

As reviewed, AMs have the ability to accomplish a wide array of functions within the lung and can consist of multiple lineages including recruited or resident macrophage, both of which may be influenced by differential polarisation. Simultaneously, surfactant is an important component of innate host defence residing in the same environment as AM. The main conclusion of the current review is that a complex interplay exists between AM and surfactant, which impacts lung homeostasis in both health and disease. Furthermore interaction of AM with the pulmonary surfactant system should be considered when interpreting data from experimental studies in which either macrophages or surfactant components are depleted, repleted or modified. The specific interactions and mechanisms by which this interaction contributes to human diseases will have to be further addressed in future studies.

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Abbreviations list

AMs, alveolar macrophages; ARDS, acute respiratory distress syndrome; DMDP, dichloro-methylene-diphosphonate; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; KO, knockout; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; TAMs, tumour-associated macrophages; TGF, transforming growth factor; T_H1, T helper 1; TNF, tumour necrosis factor.

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