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Editorial OMICS International

# Multiscale Modeling of Inflammation and Inflammatory Diseases

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## Editorial

Inflammation is an important function of the immune system to protect against pathogens and trigger specific immunity [1]. While tightly regulated inflammation is essential for host defense, clearance of damaged or transformed cells, and maintenance of tissue homeostasis, dysregulated inflammation has been associated with a number of diseases. For example, lipopolysaccharide (LPS) is a major component of the outer membrane of most Gram-negative bacteria and a potent stimulant of immune response [2]. Lipid A moiety is the endotoxic portion of LPS, binding of which to toll-like receptor 4 (TLR4), one of many pattern recognition receptors (PPRs) of the mammalian innate immune system, induces a signaling cascade via different pathways in cell and produces molecular mediators such as cytokines, leading to inflammation [3]. Excessive response to the LPS endotoxin can result in severe septic shock, a serious inflammatory disease that leads to dangerously low blood pressure and abnormalities in cellular metabolism [4]. Studies have shown that LPS transport represents an excellent target with the potential to develop compounds acting as new drugs [4]. LPS transporters belong to the ATP-binding cassette (ABC) protein family that use free-energy from ATP (adenosine 5'-triphosphate) hydrolysis, which is catalyzed by the ABC protein itself, to perform gating movements for the transport of substrates. Therefore, it is important to investigate the detailed mechanisms of how the ABC proteins perform the conformational movements and how ATP hydrolysis is catalyzed by the enzyme.

The association between chronic inflammation and cancer was first proposed by Rudolf Virchow in 1863 after the observation that infiltrating leukocytes are a hallmark of tumors [5]. It is now well recognized that although precise mechanisms are not yet fully understood, inflammation and cancer are closely correlated [6-9]. The link between inflammation and cancer development is particularly strong in patients with lung cancer, as the lungs are constantly exposed to environmental insults that may cause chronic inflammatory injuries and infection [10,11]. Currently, lung cancer is the leading cause of cancer-related deaths worldwide with 5-year survival rates averaging around only 15-18% [11,12]. Despite ongoing efforts to reduce smoking prevalence, cigarette smoking still remains the main cause of ~90% of lung cancers [13,14] with ~15% of lifetime smokers developing the disease [14]. Cigarette smoke (CS) contains more than 4,500 components including toxins, oxidants, and carcinogens [15]. Long-term CS exposure to the lung induces chronic inflammation, generating an inflammatory microenvironment for lung tumor initiation and progression [11]. CS is also the major risk factor for chronic obstructive pulmonary disease (COPD), which is the third leading cause of death globally without effective therapies [16]. COPD is characterized by progressive airflow limitation caused by airway obstruction and destruction of the lung parenchyma. There is no cure available for COPD and current drugs are mainly effective in improving symptoms and exacerbations but generally do not slow down the progression of the disease [16].

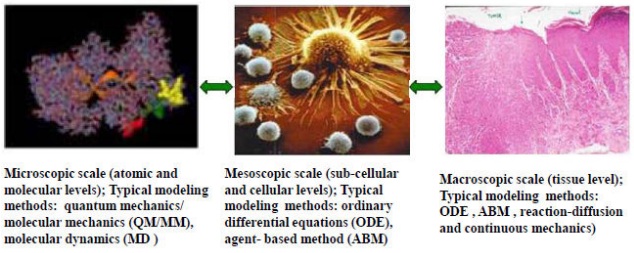


**Figure 1:** Hierarchy of scales and the related modeling approaches.

LPS- or CS-induced inflammatory responses involve innate or/and adaptive immunity and are mediated via a complex network that encompasses many molecular mediators including cytokines, multiple immune cell types and tissues, bearing a feature with multiple temporal and spatial scales (Figure 1) [17]. For instance, cytokine regulation of cell function through signal transduction usually occurs on a sub-second timescale, whereas cell production of cytokines takes minutes to hours. The LPS- or CS-induced inflammatory processes in multicellular organisms start at the atomic and molecular levels. During LPS-induced inflammation, the ABC proteins mentioned above bind and catalyze hydrolysis of ATP to drive large-scale conformational changes in the protein for the transport of LPS to the bacterial cell surface. As such, the endotoxin is exposed to and is recognized by the host innate immune cells through the PPRs on their surfaces. Similarly, pathogenic molecules in CS bind to the PPRs of innate immune cells in the lung, triggering inflammatory responses of the intracellular network. To understand the precise mechanisms of the molecular interactions requires the modeling of the system at an atomic or molecular level. Indeed, to investigate the mechanism of ATP hydrolysis catalyzed by the ABC protein, we model the reaction system at the atomic level and use a quantum mechanics (QM)/ molecular mechanics (MM) approach to calculate the reaction path of ATP hydrolysis in the protein [18]. Compare the result to that in aqueous environment [19]. Moreover, to understand how the ABC protein performs gating movements for the transport of substrates, we apply a coarse-grained modeling strategy at a molecular level and perform molecular dynamics (MD) simulations [20]. Our modeling results have demonstrated that the ABC protein is a delicate molecular machine that hydrolyzes ATP to transport substrates such as LPS across the membrane.

To model CS-induced inflammation and COPD progression, we develop a multiscale network model, in which the nodes represent

important cytokines, immune cells, and lung tissues, and the edges represent the interactions between these nodes [21]. The dynamics of the cytokines, the immune cells and tissue damage (TD) can thus be described using a set of ordinary differential equations (ODEs). Our modeling study identifies several positive feedback loops and network components playing a determinant role in the CS-induced immune response and COPD progression. The results in this modeling work demonstrate that CS-induced COPD development is a multi-step process involving both innate and adaptive immune responses. In the early acute phase of CS exposure, innate immune response predominates. During the transition from the innate to the adaptive immunity, if M1 macrophages predominate over M2 macrophages, the system proceeds to high-grade chronic inflammation and eventually toward COPD where the adaptive immunity plays a dominant role. However, when M2/Treg (regulatory T) cells are predominant over M1/Th17+CD8+T cells, the acute inflammation turns into the low-grade chronic inflammation, and COPD does not occur. The results in this study are in agreement with clinic and laboratory measurements, offering novel insight into the cellular and molecular mechanisms of COPD. This network modeling study also provides a rationale for targeted therapy and personalized medicine for the disease in future.

As mentioned above, COPD and lung cancer (LC) share the same etiological agent, CS, the link between these two diseases has gained substantial attention in recent years [21]. Epidemiological studies have observed an increased risk for lung cancer in patients with COPD [15]. Lung cancer is up to five times more frequently to occur in COPD patients than those without COPD [22]. ~50-70% of patients with lung cancer suffer from COPD [14]. A most common link between COPD and LC is chronic inflammation [11,13]. As COPD is a chronic inflammatory disorder, aberrant inflammation in COPD is critical to increase risk of lung cancer [11]. However, a question arises regarding the immune cell profiles present in COPD and lung cancer subjects. Since the features of COPD and lung cancer are diametrically opposed discussed above, the immune cell profiles for these two diseases would be quite different [13,15]. In emphysematous lungs, the predominant immune cells are polarized to be cytotoxic (often pro-inflammatory). In contrast, the immune cells in lung cancer are often anti-cytotoxic and immunosuppressive [13,15]. How this seemly contradictory cell profile is achieved in a COPD patient with lung cancer is elusive. To address this issue, we propose a network model based on the above COPD-associated one by including lung tumor (LT) and its related cells and molecular mediators as network nodes [23]. Our modeling results have shown that CS-induced chronic inflammation during COPD progression provides a microenvironment for tumor initiation and progression. In this model, several tumor-associated positive feedback loops are identified. For example, while CD8+ T cells exert antitumor effects, tumor cells can secret checkpoint molecules, the programmed death-1 ligand (PD-L1) or cytotoxic T lymphocyte antigen-4 (CTLA-4) to inhibit CD8+ T cells [24]. Thus two positive feedback loops, LT→PD-L1 (CTLA-4)CD8+T LT, form, playing an important role in lung cancer progression. Targeting these immune checkpoints, which unleashes a patient's own T cells, is revolutionizing cancer therapies [25-27].

In conclusion, inflammation is a highly complicated and dynamic process. In a living multicellular organism, it involves numerous interactions between atoms, molecules, cells and tissues. Multiscale modeling thus provides a useful tool to elucidate the mechanisms of inflammation and inflammatory diseases.

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