Pro-inflammatory and Anti-inflammatory Cytokines in Sulfur Mustard Exposed Survivors: a review

Abstract:
Aims This study reviewed the impact of sulfur mustard (SM) on the biomarkers especially the expression of pro-inflammatory and anti-inflammatory cytokines in exposed survivors after about 10 to 20 years of exposure. The review collected studies from major databases such as PubMed and Science Direct. Studies that focused on human exposure to sulfur mustard were prioritized, while studies that used mouse models were excluded to maintain a focus on its effects on human health. Sulfur mustard was associated with alteration of the expression of pro- and anti-inflammatory biomarkers Pro-inflammation such as IL-1β, IL-6, TNF-α, BDNF, GM-CSF and Anti- inflammation such as IL-4, IL-10, IL-10. The long-term effects of sulfur mustard on inflammatory biomarkers warrant further, in-depth mechanistic studies to elucidate potential therapeutic interventions targeting these pathways.

Key word: Chemical warfare, sulfur mustard, Biomarkers

Introduction:
Chemical warfare is one of the most brutal types of weapons of mass destruction, primarily using toxic agents to kill or incapacitate enemies [1]. Despite the Chemical Weapons Convention banning chemical weapons in 1993 due to the profound impact on human health and international security, some countries continue to produce them [2]. Chemical weapons are among the most inhumane warfare due to the severe acute and chronic health complications. The first large-scale use of chemical weapons after World War II occurred during the Iran-Iraq war in the 1980s. Sulfur mustard (SM) is a potent alkylating agent that binds to proteins and nucleic acids, induces cellular necrosis and leads to severe complications from inflammation to mutagenic and even carcinogenic outcomes. SM originally synthesized in 1822 and was first employed in warfare by the German army in 1917 against both Canadian and French forces, then by the British during the 1918 Hindenburg campaign. Several other nations including Spain, Italy, the Soviet Union, Japan, and Egypt utilized sulfur mustard in military conflicts. Throughout the conflict (1980–1988), the Iraq extensively used SM in lots of military operations. The use of SM verified by United Nations investigations through field assessments and clinical evaluations of exposed individuals. Ther are short- and long-term complications in various organ systems among survivors of SM exposure. The studies show that SM has different effects on the lung, skin and eyes [3]. A notable example of chemical warfare occurred during the Iran-Iraq War (1980-1988), where Iraq used sulfur mustard (SM), a potent alkylating agent that has severe health effects, including chronic inflammation and long-term complications [4]. SM could cause mild conjunctivitis in the eye, skin and pulmonary system, through delayed and severe chronic complications. Survivors may suffer from blindness, obstruction of upper airways, chronic bronchitis, and bronchiolitis in the lung and many known or unknown disorders[3]. The higher rate of health problems leads to increase the utilization of medical health services, and medical costs among chemical warfare survivors and their families over time. [5-10]
The medical expenses increase due to frequent need for hospitalizations, paraclinical, psychotherapy and rehabilitation [5].
Recent studies on sulfur mustard have shown that it alkylates cellular components and leads to the expression of a variety of inflammatory biomarkers that cause DNA damage and impaired cellular function [11]. The immune system produces inflammatory factors to fight pathogens and facilitate healing, but persistent elevation of these markers leads to chronic inflammation, which is associated with diseases such as arthritis, asthma, autoimmune disorders, neurological diseases, diabetes, cancer, conditions of aging [12], as well as, mental disorders [6]. In terms of pathology, inflammation is one of the adaptive reactions to numerous injuries from physical, chemical, and biological factors. The common signs of inflammation are related to tissues and cells responding to pathological injury induced by internal or external stimuli and damage-associated products and metabolites. The biomarkers provide important insights into the status and severity of inflammation, helping to predict patient outcomes, diagnose diseases and monitor treatment [13]. This study examined the effects of sulfur mustard

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exposure on chronic inflammatory biomarkers including pro-inflammatory, as well as anti-inflammatory cytokines in SM exposed survivors over time.

Methods:

Information of this review was obtained by searching Medline/PubMed, Science Direct, SID, Google Scholar, ISI Web of Knowledge. Keywords used for this article include: sulfur mustard, mustard gas, pro-inflammatory cytokines, anti-inflammatory cytokines, as well as, all the biomarkers related to cytokines. The keywords for pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, BDNF, GM-CSF) included: IL-1B and sulfur mustard/mustard gas, IL-6 and sulfur mustard/mustard gas, IL-15 and sulfur mustard/mustard gas, sulfur mustard/mustard gas and TNF-a, sulfur mustard/mustard gas and BDNF. The keywords for anti-inflammatory cytokines (IL-4, IL-10, IL-13) were: IL-4 and Sulfur mustard/mustard gas, IL-10 and sulfur mustard/mustard gas, IL-13 and sulfur mustard/mustard gas. The studies based on their relevance to the topic of human exposure to SM were approached and reviewed. The studies on SM exposure in mouse models have been excluded.

Inflammation is a complex biological phenomenon that resists a simple, universal definition. Depending on the context, it can be understood as a response to disturbance (such as infection), a process involving a series of defensive mechanisms aimed at eliminating the cause of that disturbance, or a state that may be pathological or protective. Each perspective highlights a different facet of inflammation. Renewed interest in the field has been driven by the recognition that inflammation is linked to nearly all human diseases. Moreover, emerging evidence shows that the cellular and molecular mediators involved in inflammation also participate in a wide array of biological functions including tissue remodeling, metabolism, thermogenesis, and even nervous system activity. There are two types of recognition of inflammatory inducers including external and internal responses that trigger the initiation of the inflammation that influence the damage in retrospective and prospective mode. The prospective mode involves the detection of potential threats before any tissue damage occurs. Pattern recognition receptors, such as Toll-like receptors (TLRs) and lipopolysaccharide (LPS) trigger inflammation. This allows the immune system to respond preemptively, even in the absence of actual pathogens, thereby limiting potential harm. Prospective recognition is advantageous because it enables early activation and potentially prevents tissue damage altogether. Similarly, other inflammatory inducers such as toxins can be recognized through their characteristic activities, allowing for early (prospective) detection and response before significant harm is done to the host [14].

Chronic inflammation is a long-term state of continuous activation of the immune system, often due to persistent infections, autoimmune diseases, or chemical irritation, which can lead to various diseases [15]. Cytokines—including interleukins, interferons, tumor necrosis factors, and chemokines—play diverse roles in modulating immune responses, exerting both pro- and anti-inflammatory effects through intricate biochemical pathways and cellular interactions. Recent advances in immunology have led to a deeper understanding of the stimuli that trigger cytokine release, their mechanisms of action, and their downstream effects on immune regulation and tissue homeostasis. Furthermore, clinical research has increasingly implicated specific cytokines in the pathogenesis of various diseases, highlighting their potential as both biomarkers and therapeutic targets. When the immune system encounters pathogenesis, it secretes inflammatory factors in two stages: pro-inflammatory factors (IL-1β, IL-6, TNF-α and BDNF) and anti-inflammatory factors (IL-4, IL-10 and IL-13). Imbalance in the expression of these factors causes chronic inflammation [16]. Cytokine levels provide insights into the presence, severity, and progression of chronic diseases. Emerging evidence suggests that inflammation is actively involved in maintaining the functional and structural integrity of tissues and organs. Understanding these physiological functions of inflammation could provide deeper insight into both the biology of health and the pathophysiology of disease. This study investigates the long-term effect of sulfur mustard on chronic inflammatory biomarkers in exposed survivors including pro-inflammatory and anti-inflammatory cytokines.

Cytokines

Cytokines are low-molecular-weight glycoproteins that play a central role in mediating immune cells and inflammation. Historically, cytokines have been classified based on their initially discovered functions

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into several subgroups, including interleukins (ILs), interferons, cytotoxic cytokines, colony-stimulating factors, chemokines, and other cytokines. Cytokines often refer specifically to interleukins produced predominantly by immune cells. These include cytokines associated with innate immunity—such as IL-1, tumor necrosis factor-alpha (TNF-α), IL-6, as well as, IL-4, IL-10, IL-13 which help regulate immune responses and maintain immune homeostasis. Cytokines are tremendously strong biological molecules, applying their effects at picogram concentrations levels. Cytokines such as IL-6, TNF-α, IL-1β, IFN-γ, IL-4, IL-10, and IL-13 are small proteins and glycoproteins that are key biomarkers of chronic inflammation, reflecting sustained immune activity and underlying disease processes. These can be assessed in biological samples to monitor inflammatory status, track disease progression, and even help treatment strategies for chronic conditions and diseases, although the routine use of them is often constrained by technical and analytical limitations [17].

1 Pro-inflammatory cytokines:

Pro-inflammatory cytokines include: IL-1β, IL-6, TNF-α, BDNF, GM-CSF. Sulfur mustard exposure has impacted on each biomarker as follow:

- **Interleukin 1β (IL-1β):**

IL-1β is a key cytokine that promotes inflammation [18]. IL-1β produced by activated macrophages and plays a fundamental role in the immune response to tissue injury and infection. IL-1β plays a role in resolving acute inflammation and higher expression of IL-1β is associated with cell injury and when the balance of IL-1 level is disrupted, it may markedly contribute to the pathogenesis of both inflammatory disease and conditions that increase the risk of developing cancer. IL-1 is an attractive molecular target to heal a wide range of diseases especially auto inflammatory diseases, autoimmune diseases, infectious disease, metabolic syndromes, ischemic diseases, and malignant tumors [19]. The effect of sulfur mustard on interleukin 1 beta (IL-1β) has been of interest as an important inflammatory marker in many diseases [20]. Studies have shown that exposure to SM increases IL-1β levels and contributes to chronic inflammatory processes, which in turn increases the risk of neurological diseases (such as stroke, brain injury, Alzheimer's disease, and multiple sclerosis) and eye diseases (such as diabetic retinopathy, glaucoma, and macular degeneration) [21-27]. This increased production of IL-1β is associated with the activation of inflammatory signaling pathways and the stimulation of immune responses, which can contribute to the development and progression of tissue damage and inflammation [28]. In clinical and preclinical studies, the toxic effects of SM on macrophages and other immune cells have been evaluated, and the results show that this substance can induce the expression of IL-1β through the NF-κB and MAPK signaling pathways [29]. These processes, in turn, can lead to serious side effects and disease progression [30, 31]. Studies have shown that Sulfur mustard leads to chronic inflammation by altering the gene expression of inflammatory cytokines, and among these cytokines, IL-1B, with its overexpression cause skin diseases [32].

- **Interleukin-6 (IL-6):**

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IL-6 is another important cytokine involved in regulating immunity and inflammation [33]. Increased IL-6 in response to sulfur mustard is associated with chronic inflammation, which is implicated in psychiatric disorders. High levels of IL-6 are associated with increased risk of psychological stress/disorders, PTSD, impairment of neuronal function/synaptic resilience, which may play a role occurrence of psychotic disorders [34]. Interleukin-6 (IL-6) has a multifaceted impact, influencing inflammation, immune responses, and hematopoiesis. Increased levels of IL-6 can weaken the body's protection against infectious diseases. Moreover, IL-6 increase insulin-stimulated glucose, proposing a role in metabolic processes. It involved in development of plaque and atherosclerosis. The effects of IL-6 have both positive and negative impacts based on the detailed biological scenario, with various physiological and pathological conditions. Increasing of IL-6 is associated with lymphoproliferative diseases, multiple myeloma, osteoporosis, and Alzheimer's disease, and can accelerate the premature aging process [35]. A cross-sectional study investigated the mental and physical health of 227 veterans exposed to sulfur mustard (SM) and 77 healthy individuals. The findings revealed that veteran's exposure to SM exhibited higher levels of anxiety, insomnia, and psychiatric symptoms compared to the controls ($P<0.05$). Interestingly, levels of interleukin-1β (IL-1β) and interleukin-6 (IL-6) were lower in the exposed group, while brain-derived neurotrophic factor (BDNF) levels were higher ($P<0.05$), indicating a possible partial improvement in their mental and physical health [36]. Another study measured interleukin-6 in two groups of exposed (60 patients with pulmonary symptoms with mild to severe complications) (n=60) and healthy non-exposed individuals (n=30). The average interleukin-6 (IL-6) concentration in the patients was found to be 0.76±0.3 picograms (pg)/ml, significantly higher than the control group's level of 0.34±0.12 pg/ml ($P=0.17$) [37]. Several studies indicated higher rate of mental health in SM exposed survivors and even their spouses, as well [38-45].

- **Tumor Necrosis Factor-alpha (TNF-α):**

Tumor necrosis factor-alpha (TNF-α) is a recognized as pro-inflammatory cytokine with diverse biological effects. TNF-α regulate inflammation, host defense, immunity/autoimmunity, apoptosis, carcinogenesis and organ development. TNF is recognized as a key mediator of inflammatory and immune responses. TNF signals to immune cells that kill tumor cells. TNF has an important role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease(IBD). TNF-α acts as an arbitrator of the local tissue environment after injury. It can initiate apoptosis, regulate cell survival and proliferation and tissue regeneration and remodeling. Excessive amounts of cytokines cause widespread inflammation that damages organs and tissues [46]. Sulfur Mustard is a blistering agent with damaging effects on the skin, eyes, and respiratory system. One of the main mechanisms of its toxicity is the induction of an inflammatory response in which TNF-α (tumor necrosis factor alpha), a key pro-inflammatory cytokine, plays an important role [47]. Exposure to sulfur mustard can increase the expression and secretion of TNF-α from various cells, including keratinocytes, macrophages, and lymphocytes [48]. This, raise the risk of some chronic connective tissue disorders with endothelial dysfunction, fibrosis, cancer, and premature aging. This finding is consistent with previously published studies indicating that sulfur mustard (SM) acts as a carcinogen even after a single exposure, regardless of the dose or duration of exposure [9]. Chemical warfare victims with eye and lung injuries experience significantly more psychological disorders and poor quality of life, and limitations in daily activities. This is largely determined by persistent lifelong symptoms caused by both irreversible and progressive health complications. Poor outcomes are further influenced by factors including the severity of the initial injury, the presence of comorbid conditions, and associated psychological disorders [44, 45, 49-54].

- **Brain-derived neurotrophic factor (BDNF):**

Among all neurotrophic factors, brain-derived neurotrophic factor (BDNF), plays a crucial role in promoting neurogenesis, neuronal survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity (essential for learning and memory). BDNF regulates energy metabolism, glucose and avoids β cells exhaustion. Decreasing the levels of BDNF commonly associates

with neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis). BDNF help to prevent and manage diabetes mellitus, as well [55]. The exposure to sulfur SM has been shown to adversely affect brain-derived neurotrophic factor (BDNF) levels, which are crucial for neuronal survival, growth, and function [56]. Limited studies have also shown that Sulfur mustard can induce neuro-inflammation and oxidative stress, leading to decreased BDNF expression [57, 58]. This reduction in BDNF may impair neuroplasticity and cognitive functions, highlighting the potential long-term neurological consequences of sulfur mustard exposure [59]. In only one study it has been showed that the level of BDNF in serum were elevated [36].

When individuals are exposed to sulfur mustard, the resultant inflammation and oxidative stress can disrupt the normal expression of BDNF [60]. Survivors exposed to sulfur mustard exhibit varying levels of this biomarker, and this imbalance may lead to psychiatric disorders and central nervous system diseases [61]. This disruption can result in lower levels of BDNF in the brain, leading to several potential consequences: first, can activate inflammatory pathways in the central nervous system. This inflammation can create an unfavorable environment for neurons and adversely affect BDNF signaling [62]. Second, reduced BDNF levels are associated with impaired cognitive functions, such as learning and memory. Individuals exposed to sulfur mustard may experience difficulties in these areas due to lower neuroplasticity [63]. It may have long-lasting implications, potentially leading to chronic neurological issues, including neurodegenerative diseases or cognitive decline [64]. Moreover, BDNF plays a significant role in the aging process [65]. Overall, the impact of sulfur mustard on BDNF levels underscores the need for further research to understand its effects on brain health and the mechanisms involved.

- **Granulocyte-macrophage colony-stimulating factor (GM-CSF)**:

GM-CSF is a growth factor that stimulates myeloid progenitor cells. Produced by various cells (T cells, phagocytes, etc.), GM-CSF enhances immune responses by generation of myeloid cell subsets including neutrophils, monocytes, macrophages, and dendritic cells in response to stress, infections, and cancers and activating immune cells such as dendritic cells (DCs) and plays a critical role in regulating myeloid cell host defense [66]. The DCs, along with macrophages and monocytes, are antigen-presenting cells (APCs) whose function is enhanced by GM-CSF. GM-CSF works alongside the other inflammatory cytokines (IL-1α, IL-1β, TNF-α, IL-6, IL-8) in the regulation of immunity and inflammation [67]. GM-CSF abnormal level (both low or high level), can worsen autoimmune diseases and inflammation, can weaken immunity and impair wound healing, elevated GM-CSF has been shown to contribute to inflammation in inflammatory arthritis, osteoarthritis, colitis asthma, obesity, and COVID-19[68], as well as, accelerate aging[69]. The specific dangers depend on the extent and cause of the imbalance[70]. A study investigating the role of cytokines in sulfur mustard-induced pulmonary fibrosis, bronchoalveolar lavage (BAL) fluid from 18 sulfur mustard-exposed veterans with pulmonary fibrosis (PF) and 18 control subjects was examined. Significantly higher levels of G-CSF and GM-CSF were found in the BAL fluid of exposed patients compared with controls. IL-8 levels were also significantly elevated. In addition, IL-8 and G-CSF levels were correlated with neutrophil counts, while GM-CSF levels were correlated with eosinophil counts in the BAL fluid of the SM exposed patients. The findings suggest that neutrophilic alveolitis, eosinophilia, and increased IL-8, G-CSF, and GM-CSF in BAL fluid are associated with the development of fibrosis in sulfur mustard victims [68]. In a cohort study in Sardasht, Iran, the effect of sulfur SM on GM-CSF levels was investigated in two groups of exposed (n=369) and unexposed(n=125) after 20 years. This study reported that serum GM-CSF levels were not significantly different between exposed and unexposed subjects. However, a positive correlation was observed between GM-CSF and eosinophil counts in the exposed group. Furthermore, the results of this study showed that there was no significant association between GM-CSF levels and pulmonary function parameters [71].

2. Anti-inflammatory cytokines:

- **Interleukin-4 (IL-4):**

Like many cytokines, Interleukin-4 (IL-4) be able to affect a numerous target cell in several ways. IL-4 has a significant role in developing effector T-cell responses, regulating antibody production, hematopoiesis and inflammation. Interleukin-4 (IL-4) is a cytokine that plays a crucial role in the immune system, primarily involved in promoting the differentiation of naive T cells into T-helper 2 (Th2) cells [72]. IL-4 is also essential for the production of immunoglobulin E (IgE) and the activation of mast cells and eosinophils, which are key players in allergic responses and asthma. Overproduction of IL-4 causes hyper-activation of lymphocyte, elevation of IgE, and autoimmunity [73]. Following exposure to sulfur mustard, there is evidence suggesting an increase in IL-4 levels due to its pro-inflammatory effects [74, 75]. Recent studies have highlighted the role of IL-4 in mediating the Th2 response in models of chemical exposure, including sulfur mustard [76]. This increased IL-4 production can contribute to a broader inflammatory response, exacerbating tissue injury and promoting airway hyper responsiveness [77]. Understanding the modulation of IL-4 following sulfur mustard exposure is essential for developing therapeutic strategies aimed at managing inflammation and other related respiratory conditions [78]. Veterans exposed to sulfur mustard have high levels of IL-4, This substance increases the production of IgE (a type of allergy-related antibody), leading to severe inflammation in the lungs and other tissues, ultimately leading to tissue damage [79].

- **Interleukin-10 (IL-10):**

Interleukin (IL)-10 is well-known for its potent anti-inflammatory and immunosuppressive effects and recognized as a product of T helper 2 cells. IL-10 is now known to be produced by various myeloid- and lymphoid-derived immune cells participating in both innate and adaptive immunity. Interleukin-10 (IL-10) has essential role in modulating inflammation and in maintaining cell homeostasis. It acts as an anti-inflammatory cytokine and protects from an uncontrolled immune response and has immune stimulating functions. IL-10 is a potent anti-inflammatory cytokine that functions to inhibit the expression of pro-inflammatory cytokines. Imbalance and over activity of IL-10 can indirectly damage various tissues in the body by suppressing the immune system, promoting the growth of cancer cells, and impairing wound healing [80]. Recent researches suggest that while IL-10 is increased following sulfur mustard injury, an imbalance in favor of inflammation can reduce the protective effects of IL-10, leading to long-term tissue damage and altered immune responses [81, 82]. In one study, the levels of the cytokines TNF-α in tears and IL-1α, IL-1β, IL1Ra, IL-6, TNF-α, GM-CSF, and FasL in the serum of 128 SM-exposed veterans with severe ocular injury were compared with 31 healthy controls. The results showed that in SM-exposed veterans, meibomian gland dysfunction (MGD), decreased tear breakup time (TBUT < 10 seconds), and conjunctival, limbal, and corneal abnormalities were more common. The severity of ocular injury was mild in 14.8%, moderate in 24.2%, and severe in 60.9%. Serum levels of IL-1α and FasL were significantly higher in veterans, and serum and tear levels of TNF-α were significantly lower than in controls ($P<0.001$). Serum levels of FasL were significantly higher in cases with severe ocular injury than in controls ($P=0.03$). There was no significant difference in serum levels of IL-1β, IL-1Ra, IL-1α/IL-1Ra, and IL-6 between the two groups. Finally, increased serum levels of IL-1α and FasL may contribute to the development of ocular surface abnormalities in patients exposed to SM, and the decrease in TNF-α in tears is likely due to the decrease in serum levels of this cytokine [83]. Similar study indicated that the incidence rate of cancer was significantly increased in SM exposed survivors. The incidence rate ratio of cancer for SM exposure was 2 times higher than general population. This study suggests carcinogenesis of SM following acute exposure to SM in the victims after 20 years of exposure [9].

- **Interleukin-13 (IL-13):**

IL-13 is an anti-inflammatory cytokine that regulate IgE synthesis, goblet cell hyperplasia, mucus hypersecretion and causes airway hyper responsiveness. IL-13 is an important mediator for allergic inflammation, asthma and atopic dermatitis. IL-13 has effects on immune cells. It is suspected that IL-13 is the core mediator of the physiologic changes made by allergic inflammation in a lot of tissues. IL-13 it is involved in various processes such as airway remodeling, fibrosis, and the regulation of mucus production. High levels of Interleukin 13 (IL-13) indicate that immune system is overactive. This could be a response to an ongoing infection or disease that body is trying to fight off [84]. Following exposure to sulfur mustard, IL-13 levels may be increased or decreased, with increased IL-13 levels being associated with asthma, allergies, fibrosis, and inflammatory bowel disease. The decreased level of IL-13

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is associated with increased risk of infection and impaired wound healing [85]. Recent studies have shown that IL-13 is often upregulated in response to airway irritants and is linked to the pathophysiology of conditions such as asthma [86]. In the context of sulfur mustard exposure, increased IL-13 levels can exacerbate bronchoconstriction and contribute to long-term respiratory sequelae [87]. Treatment Targeting IL-13 could mitigate the adverse effects associated with sulfur mustard-induced inflammation.

Conclusion:

Studies have proven that sulfur mustard leads to significant changes in inflammatory markers such as pro-inflammatory (e.g., TNF-α, IL-1β, IL-6) and anti-inflammatory cytokines. These changes indicate activation of the innate immune system and initiation of a severe inflammatory response. SM exposure leads to activation of inflammatory signaling pathways such as the NF-κB pathway, which ultimately increases the production of further pro-inflammatory cytokines. These changes appear to be a regulatory mechanism to control the initial severe inflammatory response and prevent further tissue damage.

Overall, SM causes a significant imbalance in both inflammatory and anti-inflammatory biomarkers. An initial and dominant increase in pro-inflammatory biomarkers causes widespread tissue damage. While the subsequent increase in anti-inflammatory biomarkers, which acts as a compensatory mechanism, is not sufficient alone to reduce the damaging effects of inflammation. This imbalance in biomarkers is one of the important factors in the development of long-term complications after sulfur mustard exposure. These complications include chronic respiratory, skin, and eye diseases, as well as an increased risk of cancer. A numerous factors including age, sex, adiposity status and overall inflammatory state that could affect the circulating levels of cytokines [88].

Therefore, it should be considered that other than SM, cytokines could be also influenced by some of these factors. Future studies focus on the advanced development of the predictive biomarker modeling framework that can extract predictive biomarkers from complex data, beside, combining biomarkers from different sources (imaging, molecular, clinical) can better improve the accuracy of SM outcome predictions.

- **Multimodal Biomarker Panels:**

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