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Authors

Yang, David C
Chen, Ching-Hsien

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Cigarette Smoking-Mediated Macrophage Reprogramming: Mechanistic Insights and Therapeutic Implications

David C. Yang[1,2] and **Ching-Hsien Chen**[2,3,*]

[1]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine and Center for Comparative Respiratory Biology and Medicine, University of California Davis, Davis, California, USA.

[2]Division of Nephrology, Department of Internal Medicine, University of California Davis, Davis, California, USA.

[3]Comprehensive Cancer Center, University of California Davis, Davis, California, USA.

Abstract

Macrophages, the mature form of the monocytes, play a significant role in tissue homeostasis and immunity. In response to environmental cues, they can undergo classical or alternative activation, polarizing into specialized functional subsets. A common hallmark of the pathologic environment is represented by cigarette smoking. Although the contribution of cigarette smoke to various cellular processes has been extensively studied, its roles in macrophage polarization have been conflicting. This review discusses the molecular and functional differences of cigarette smoke-exposed macrophages that exist between pro-inflammatory and anti-inflammatory states. We also highlight the most recent advances in therapeutic potential of targeting signaling molecules associated with smoking to modulate macrophage plasticity and polarized activation.

Keywords

Cigarette Smoking; Signaling Molecules; Inflammation; M1/M2 Macrophages

Introduction

Macrophages are an abundant immune cell type that play multiple important roles in various tissues throughout the body. Present in all tissues, these immune cells play roles in maintaining tissue homeostasis, response to various external signals such as infection and cell damage from external toxicants, and metabolic and developmental functions (1). To respond to these environmental cues, macrophages display a degree of plasticity and can acquire distinct phenotypes in response to certain stimuli. Classically, the “activated” macrophages are thought of as being divided into two distinct groups: M1 and M2 type macrophages. Like the Th1 and Th2 classifications in T-helper cells, from which the

*Corresponding Author. Ching-Hsien Chen Ph.D., Division of, Nephrology, Department of Internal Medicine, University of, California Davis, Davis, CA 95616, USA., Tel: 530-752-4010; FAX: 530-752-3791, jchchen@ucdavis.edu,.

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classifications were derived, M1 and M2 macrophages are described as inflammatory (killing) and anti-inflammatory (repairing) (2). These macrophages release a variety of cytokines and chemokines that contribute to these functional processes. Although is tempting to simply classify macrophages neatly into these two groups, many studies suggest that macrophages display a spectrum of phenotypes that do not fall neatly into each category (3, 4). As such, to reflect the diversity of phenotypes displayed by these cells in various pathological conditions, we will address these macrophages as “Ml-like” and “M2-like” macrophages.

In the present review, we present the current findings and offer insights into the current state of the field on the role of cigarette smoke in macrophage polarization. Cigarette smoking has been shown to be able to affect macrophage function and phenotype (5–12). Thus, in this review, we define M1/M2 macrophage activation and the role of cigarette smoke in macrophage function and phenotype. We also explore the specific contributions of the signaling molecules involved in cigarette smoke-exposed macrophages and elucidate the unique ways in which they confer reprogramming of macrophages. Finally, we speculate on ways to target polarized macrophages to combat cigarette smoking-related illness. To address how cigarette smoke affects macrophages mechanistically to provide a concise overview, we highlight the effect of cigarette smoke on three main pathways that influence macrophage phenotype and activity: the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway, the mitogen-activated protein kinase (MAPK) signalling pathway, and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway.

The M1 and M2 Paradigm of Macrophage Activation

M1 and M2 macrophages are activated in different ways and respond according to the stimuli presented (2, 3). M1 macrophages are driven by exposure of macrophages to microbial products such as lipopolysaccharide (LPS) and other toll-like receptor (TLR) ligands and by pro-inflammatory cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). These stimuli result in increased antigen presentation, increased nitric oxide (NO) and reactive oxygen species (ROS) production, and drives heightened production of many inflammatory cytokines such as interleukin 12 (IL-12), interleukin 23 (IL-23), TNF-α, interleukin 1 beta (IL-β), interleukin 6 (IL- 6), type I IFN, and chemokines CXCL1–3, CXCL-5, CXCL8–10. These pro-inflammatory cytokines inhibit cell proliferation and damage contiguous tissues. The simultaneous increase in NO/ROS in addition to the release of many pro-inflammatory cytokines defines the M1 phenotype. In contrast, M2 macrophages are driven by anti-inflammatory cytokines including interleukin 4 (IL-4), interleukin 10 (IL-10), or interleukin 13 (IL- 13) and epitopes associated with cell damage or parasitic infection. M2 macrophages display a more “repair-like” phenotype that is characterized upregulation of Dectin-1, dendritic cell-specific intercellular adhesion molecule-3-grabbing non integrin (DC-SIGN), mannose receptor, scavenger receptors A and B-1, cluster of differentiation 163 (CD163), C-C chemokine receptor type 2 (CCR2), IL-8 receptors alpha and beta (CXCR1–2), matrix metalloproteinases (MMPs), IL-10, tumor growth factor beta (TGF-β) and produces ornithine and other polyamines associated with tissue repair (13–15).

Role of Cigarette Smoke in Macrophage Function and Phenotype

Of the many environmental stimuli that macrophages are exposed to, one that is prevalent is cigarette smoke, which damages the lung and can lead to a variety of pathologies including chronic obstructive pulmonary disease (COPD), asthma, and pulmonary fibrosis (16–18). In these disease types, the role of macrophages have been shown to play a significant role in modulating inflammation and dysregulated repair processes (19). The significance of the role of macrophages in the context of cigarette smoke is further strengthened by the observation that almost all smokers have an accumulation of macrophages in the lungs (20). Many studies have shown that exposure to cigarette smoke modulates inflammation, macrophage phenotype, and alters many macrophage functions such as phagocytosis of microbes (6–11). Interestingly, smoking was found to inhibit macrophage response to infection (8, 10, 11). Van Zyl-Smit et al demonstrated that upon exposure to cigarette smoke extract (CSE), cytokine responses to infection by mycobacterial were inhibited (11). Although phagocytic function of the macrophages was not impaired beyond very short term (4 hours), production of cytokines involved in inflammation (IFN-γ, TNF-α, and IL-10) were significantly reduced in macrophages exposed to cigarette smoke. Another study by Shaykhiev et al showed that macrophages from smokers with COPD display a downregulated M1-like phenotype with a decrease of multiple inflammatory cytokines such as IL-1β and IL-18 and upregulated M2-like characteristics such as expression of matrix metalloproteinases, which are involved in tissue remodeling (9). Additionally, Phaybouth and colleagues' experiments suggested that exposure to cigarette smoke in neonatal mice reduces inflammatory response to viral infection marked by reduced levels of IFN-γ and IL-12 (8). In addition to affecting the cytokines expressed and secreted by macrophages, smoking has also been shown to affect cell activities, in agreement with Park et al's observation that cigarette smoke condensate reduces cell viability and damages various cellular organelles including the mitochondria, endoplasmic reticulum, and lysosome (7). This is also associated with an induced expression of cell damage and apoptosis proteins. A study by Eapen et al showed that although in the lung the M1- like phenotype is more dominant in COPD patients with smoking history, there is a promotion of M2-like macrophages in the airway lumen (21). Another study of COPD patients by Dewhurst et al showed that smoking and COPD promotes certain populations of macrophages displaying M2-like phenotypes (22). Overall, these studies suggest that there is a downregulation of the M1-like phenotype after exposure to cigarette smoke or CSE and a review of the role of alveolar macrophages in COPD had noted similar findings (23).

However, there are some studies that demonstrate the opposite effect. A report by Yang et al points to higher levels of pro-inflammatory cytokines in CSE-treated macrophages (12). This study is supported by Karimi et al's observation that expression of the inflammatory cytokine IL-8 is increased after exposure to CSE (5). In contrast to the study by Shaykhiev et al, Kunz et al found that in current smoker COPD patients, there is a predominance of pro-inflammatory macrophages compared to those in the lungs of ex-smoker COPD patients. In the same study, a promotion of M2-like macrophages was shown in the airway lumen of COPD patients with smoking history, whereas abundant M1-like macrophages were observed in the airway wall (21).

These drastically opposite findings highlight a current debate in the field concerning effect of cigarette smoke on the pro- inflammatory and anti-inflammatory response. A more in-depth review of this divide in opinion was published by Smith et al which delves into the methodologies, types of disease studied, and more utilized by different groups investigating the effect of cigarette smoke on macrophages. They found that the field is divided almost evenly between the two stances suggesting that there is no consensus concerning the role cigarette smoke plays in mediating inflammatory response (24). As suggested by Smith et al, this may be due to a variety of factors. Many studies investigate the initiating stimuli in normal cells (e.g. exposing normal macrophages to CSE). This contrasts with many disease states when the current pathological state is well past the initial exposure stage and inflammation may have already occurred and subsequently worsened or subsided. A notable example of this are the studies by Shaykheiv et al and Kunz et al where the former study only included mild disease compared to the latter study which incorporated a more comprehensive cohort of patients, resulting in different findings by each group. Another issue that may be a confounding factor is the disease types investigated in many studies. Some are focused on COPD whereas others are focused on recurrent microbial infections such as tuberculosis. Given that these disease states are vastly different and involve different responses (tissue-repair and inflammation respectively), the effects of cigarette smoke on these diseases may vary. Lastly, there is also a great variability in study design and procedure. Many studies utilize different cigarettes, extraction procedures, and exposure procedures. Different extraction procedures can lead to differing amounts and types of compounds extracted from cigarette smoke and different exposure protocols can also contribute to the amount and variety of compounds cells are exposed to. As we are primarily more interested in the signaling mechanisms of cigarette smoke in macrophages, the investigation of the variability of procedures and materials used is beyond the scope of this review and a more in-depth look into the variability of procedures can be found in Smith et al's review article (24).

Signaling Molecules Involved in Cigarette Smoke-Mediated M1/M2 Polarization

Several signaling pathways identified to date have been implicated in cigarette smoke-mediated macrophage polarization. The most well-described cigarette smoke-mediated pathways involve NF-κB, mitogen-activated protein kinase (MAPK), and JAK/STAT signaling. These pathways are the main pathways that regulate the production of many pro-inflammatory and anti-inflammatory cytokines and other proteins that define M1-like and M2-like macrophages. A schematic diagram of cigarette smoke-activated signaling pathways is shown in Figure 1.

In addition to the signalling molecules discussed below, one of the most well studied signalling molecules modulated by cigarette smoke is the nicotinic acetylcholine receptors (25). Studies have shown that these receptors are able to inhibit inflammatory cytokine production when activated (26–28). These effects are modulated through activation of JAK/STAT and inhibition of NF-κB (26). The activation of these receptors has been demonstrated to induce an M2-like phenotype in macrophages (29, 30). Given that these receptors signal through many of the signalling molecules discussed below, we will not focus on the nicotinic

acetylcholine receptors for this review and instead investigate the role of smoke on NF-κB, MAPKS, and JAK/STATs.

NF-κB Signalling—NF-κB is a protein heterodimer that consists of two subunits, p50 and p65. In its inactive state, NF-κB is bound to IκB which prevents the protein from translocating to the nucleus and acting as a transcription factor. NF-κB can be activated by toll-like receptors (TLRs), TNF-α, reactive oxygen species (ROS), and inflammatory cytokines. Upon activation by certain stimuli such as LPS through toll-like receptor 4 (TLR4), IκB is phosphorylated and subsequently degraded. Due to IκB degradation, NF-κB is released and translocates to the nucleus and induces expression of its canonical target pro-inflammatory genes. Since NF-κB controls expression of a variety of inflammatory cytokines, modulation of its activity by cigarette smoke is a significant factor in macrophage phenotype (Table 1).

A study by Chen et al demonstrated that in smokers' alveolar macrophages, there is a decrease of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-8, and reduced TLR2 and TLR4 signaling as a result of impaired activation of NF-κB (31). Another study conducted by Zhong et al showed that NF-κB activity is reduced in rats exposed to cigarette smoke and induced an increase of apoptosis in alveolar macrophages (32). The inhibitory activity of cigarette smoke is supported by findings from Kim et al which showed that hydroquinone, a compound found in cigarette tar, is able to reduce IL-12 production in response to LPS in mouse macrophages and RAW 164.7 monocytic cells through NF-κB inhibition (33).

In contrast, TLR4/NF-κB activity was reported to be induced upon treatment with CSE, leading to high levels of IL-8 secreted by macrophages (5). This observation is supported by other findings in the field that CSE increases NF-κB activity and thereby up-regulates the levels of inflammatory cytokines such as IL-1β and TNF-α (34, 35). Of note, a study conducted by Wang et al showed that four months of cigarette smoke exposure increases NF-κB activity coincident with elevated levels of pro- inflammatory cytokines in rats (34).

Taken together, cigarette smoke seems have conflicting roles in modulating NF-κB activity. However, it must be mentioned that the studies that found increased NF-κB activity primarily looked at low dosages of CSE or condensate in previously untreated cells. This indicates that although cigarette smoke is more likely to predispose macrophages to an M1-like phenotype, this may not be the case in the long term. CSE has also been shown to inhibit cell proliferation and cause apoptosis with high levels of CSE reducing NF-κB activity. Furthermore, as seen in the study by Chen et al, in the state of established disease, cigarette smoke seems to induce a more M2-like phenotype (31). This suggests that in the initial stages before disease onset, inflammation occurs due to cigarette smoke but during the stage of established disease, the effect is reversed, and smoke may contribute to a M2-like phenotype.

MAPK Signalling—MAPKs are signaling molecules downstream of many cell receptors and regulate a wide array of cellular activities including cytokine production and regulating cellular phenotype. Various studies have shown a spectrum of effects that cigarette smoke can play on MAPK signaling in macrophages.

CSE has also been found to activate ERK, a signaling molecule part of the MAPK signaling pathways, and induce expression of mucin MUC1 and TNF-α and that these activities can be attenuated by targeted inhibition of ERK activity (36, 37). A study in support of these findings by Koch et al showed that in response to LPS in smoker lung macrophages, there was an increased production of the pro-inflammatory cytokine IL-8 which was ERK modulated (38). The role of MAPK in promoting inflammation is further strengthened by Marumo et al who showed that cigarette smoke-induced lung inflammation is p38-dependent and that inhibition of p38 reduces inflammation as marked by reduced TNF-α, IL-1β, and neutrophil infiltration (39).

In opposition to these findings, Metcalfe et al demonstrate that mice exposed to cigarette smoke had reduced reactive nitrogen species (RNS), TNF-α, and IL-12 due to reduced JNK, another component of the MAPK signaling (40). This is due to direct alkylation of JNK by acrolein, an electrophilic compound found in cigarette smoke, inhibiting MAPK signaling. Yet another study by Hristova et al shows that in COPD macrophages, exposure to cigarette smoke inhibits p38 and p65 MAPK activation, resulting in reduced inflammatory response through TLRs (41). Additionally, the report by Chen et al where reduced NF-κB activity was observed also noted decreased P38 and IRAK, which are upstream of JNK (31).

These results indicate that MAPKs maybe play differential roles in response to cigarette smoke based on whether this is pre-existing disease and the length of exposure. As seen in the first two studies, the time of exposure was relatively short compared to the studies by Metcalfe et al and Hristova et al which included a four-month exposure of mice to cigarette smoke and macrophages derived from COPD patients who already have disease and may have been smokers in the past. The current data suggest the possible function of MAPKs in mediating short term inflammation (M1-like) in response to cigarette smoke. However, it should be noted that MAPKs may be inhibited by cigarette smoke in later stages of diseases and lead to a more M2-like phenotype. This could possibly be explained by cigarette smoke inducing short term activation of MAPK signalling that is reduced over time to changes to cell phenotypes and genes.

JAK/STAT Signalling—JAK/STAT signaling is an important pathway that modulates cellular response to cytokine stimulation. Upon activation by receptors bound to ligands, JAK proteins are phosphorylated, in turn phosphorylating and activating STAT proteins. STATs then dimerize and translocate to the nucleus leading to expression of target genes. In the context of cigarette smoke, macrophages seem to be potentiated to a M2-like phenotype. This phenomenon can be observed in a recent study showing that CSE is able to induce IL-13/STAT6 signaling resulting in an M2-like macrophage phenotype (42), a conclusion supported by Yuan et al's study, which demonstrates an inhibitory effect of CSE on the levels of ROS/RNS and TNF-α. A panel of five cytokines, IL-12, IL-10, IL-6, and TGF-β, were shown to increase concomitantly with JAK2/STAT3 activity induced by CSE (43). There is further support for this phenomenon by Geraghty et al that STAT3 was activated in mice exposed to cigarette smoke and resulted in increased anti-inflammatory proteins and MMPs (44). Of interest, macrophages from smokers were documented to exhibit a reduction in STAT1 activity, leading to the downregulation of IFN-γ signaling (45). Considering the variety of STATs modulated by cigarette smoke, it would be reasonable to assume that

certain STATs associated with an M2-like phenotype (STAT3 and STAT6) are active in response to cigarette smoke, whereas STATs associated with M1-like phenotype (STAT1) is decreased after cigarette smoke exposure.

Therapeutic Potential of Targeting Macrophage Polarization

Since the effects of cigarette smoke are propagated by cell signaling proteins and in light of macrophages polarized toward different phenotypes in various diseases, there is an opportunity to target these aberrantly polarized cells with specific therapeutics. This involves in defining whether the macrophages participate in a specific disease. The growing body of pre-clinical evidence has demonstrated that macrophage polarization process is a feasible therapeutic target and targeting its relevant pathways deserves more in-depth investigations for the development of novel drugs. Currently, much focus is on controlling inflammatory diseases such as atherosclerosis and rheumatoid arthritis. Although a plethora of anti-inflammatory drugs such as corticosteroids are currently available that can target many of the cytokines and signal molecules involved in inflammatory M1-like macrophage polarization, many of these drugs lack specificity and do not affect macrophages to a great degree. However, there are therapeutics that show potential to target both M1 and M2 polarized macrophages. These include targeting the JAK/STAT pathways, macrophage recruitment, macrophage depletion, and macrophage polarization via targeting various receptors and pathways. Of interest are therapies targeting STATs and NF-κB which have shown promise in targeting M1-like and M2-like macrophages respectively (46, 47). In addition, there is some promise in utilizing tyrosine kinase inhibitors in targeting aberrantly activated macrophages (46, 48). However, with TKIs, there is the possibility of compensatory pathways and the off-target effects that may hinder therapeutic efficacy. A more in-depth review of these potential therapeutics is presented in Poh and Ernst's review article (49).

Concluding Remarks

Macrophages are an important cell type that play a wide variety of roles in various organ sites. Through modulating expression of pro-inflammatory and anti-inflammatory factors in response to different environmental stimuli, macrophages can exert a variety of effects in different disease types. Cigarette smoke, one of the most prevalent environmental factors, can have a wide spectrum of effects on macrophages. Cigarette smoke has been shown to suppress phagocytic ability in macrophages in response to infection. From the current findings in the field, it is reasonable to expect that cigarette smoke exerts an anti-inflammatory role and promotes a M2-like phenotype. These effects are mediated through a few major pathways including the NF-κB, MAPK, and JAK/STAT signaling pathways. Many studies suggest that targeting macrophages through these pathways may ameliorate diseases characterized by polarized macrophages (46, 47, 50–52). Reversal of these polarized macrophages could lead to innovative therapies where the secreted cytokines promoting disease can be attenuated and disease progression can be halted. Continual research into the molecular pathways altered by cigarette smoke and their role in promoting disease may yield more specific therapies to target macrophages and may translate into promising new approaches to tacking macrophage activities in disease.

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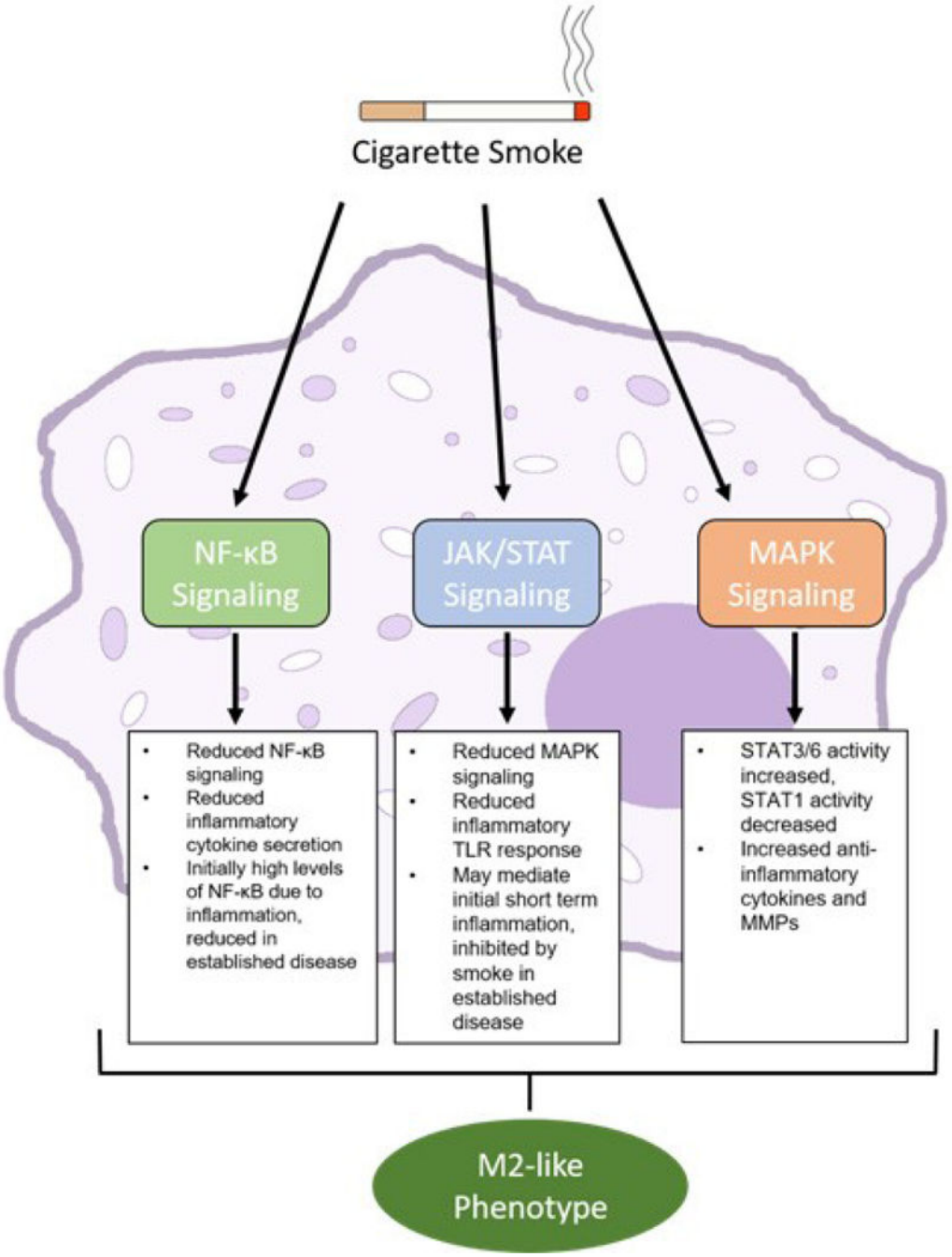

Figure 1.

Overview diagram of cellular pathways altered by cigarette smoke. Cigarette smoke has been shown to alter the signal activity of a variety of pathways (NF-KB, JAK/STAT, and MAPK) and subsequently influence cytokine production and mediate inflammation. Alterations of these pathways participate in both short-term and long-term diseases.

Table 1.

Overview diagram of signalling molecules altered by cigarette smoke. Cigarette smoke has been shown to alter the activity of an array of signalling molecules (NF-KB, JAK/STAT, and MAPK) and consequently modulate cytokine production and phenotype.

Signalling Molecules Modulated by Smoke	Effect on Phenotype and Cytokine Production	References
↑Nicotinic Acetylcholine Receptor activity	↑M2-like phenotype ↓TNF-α, IL-6, IL-12, IFN-γ	26–30
↓NF-κB activity	↓TNF-α, IL-1 β, IL-6, IL-8, IL-12	31–33
↑NF-κB activity	↑TNF-α, IL-1 β, IL-8	5, 34–35
↑ERK activity	↑MUC1, TNF-α, IL-8	36–38
↑p38 activity	↑TNF-α, IL-1 β, neutrophil infiltration	39
↓JNK activity	↓NF-α, IL-12	40
↓p38 and p65 activity	↓Inflammatory response, NF-κB activity	31,41
↑JAK/STAT activity	↑M2-like phenotype, IL-5, IL-10, IL-12 ↓TNF-α, ROS, NOS, IFN-γ activity	42–45