

## Inflammatory features of obesity and smoke exposure and the immunologic effects of exercise

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### ABSTRACT

*Many lifestyle-related diseases, such as obesity and cigarette smoke-induced pulmonary morbidities, are associated with chronic systemic inflammation, which has been shown to contribute to the disease initiation and progression, and also for co-morbidities of these diseases. While the source of inflammation in obese subjects is suggested to be mainly the visceral adipose tissue, smoke-induced inflammation originates in the pulmonary system. Here, chronic cigarette smoking induces oxidative stress, resulting in severe cellular damage. During obesity, metabolic stress pathways in adipocytes induce inflammatory cascades which are also accompanied by fibrotic processes and insulin resistance. In both diseases, local inflammatory signals induce progressive immune cell infiltration, release of cytokines and a subsequent spill-over of inflammation to the systemic circulation. Exercise training represents an effective therapeutic and immune regulating strategy for both obese patients, as well as for patients with smoke induced pulmonary inflammation. While the immune-regulating impact of exercise might primarily depend on the disease state, patients with pulmonary inflammation seem to be less responsive to exercise therapy. The current review tries to identify similarities and differences between inflammatory processes, and the consequences for the immunoregulatory effects of exercise as a therapeutic agent.*

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### 1. INTRODUCTION

Many lifestyle-related diseases—such as diabetes type II, coronary heart disease (CHD), cancer, obesity or chronic obstructive pulmonary disease (COPD)—are associated with chronic systemic inflammation. Beyond mutual association, systemic inflammatory processes have been shown to contribute to the initiation and progression of these diseases (1), and are suggested to be an important reason for their shared comorbidities. Most of these diseases share some similarities in their inflammatory genesis, while other related processes are distinctly different. A combination of two or more of these diseases has been shown to further aggravate morbidity and mortality (2). Exercise is known to be an effective treatment for most of these diseases, at least partly due to its immune-regulating properties (3).

In this regard, it has been shown that patients with specific diseases, such as chronic obstructive pulmonary disease (COPD), are less responsive to exercise therapy compared with other diseases, such as obesity (4). However, until now, there are few data available to prescribe different exercise guidelines for specific disease conditions characterized by a dysregulated immune system. In order to better understand the inflammatory pathophysiological genesis of lifestyle-related diseases, the current review tries to compare the inflammatory processes at work in two examples of highly prevalent life style-related diseases: obesity and long-term cigarette smoking. Knowing the specific cellular and molecular mechanisms of inflammation initiation and progression will enable more precise and safe application of exercise therapy for each disease and individual case.

### 2. SYSTEMIC LOW-GRADE INFLAMMATION DURING OBESITY

Obesity is a major global health issue. The World Health Organization (5) update (2016) showed that around 39% of people over 18 years were overweight (BMI >25 kg/m<sup>2</sup>), while 13% were obese (BMI >30 kg/m<sup>2</sup>). Obesity increases the risk of mortality (6,7) through its strong association with other comorbidities, such as Type 2 diabetes mellitus (T2DM), cardiovascular diseases, insulin resistance, non-

alcoholic fat liver disease (NAFLD), osteoarthritis, and autoimmune diseases (7,8). In addition to their personal burden, these disease have deep economic and social impacts on Western society (9).

Obesity development depends on different factors, including genetic, epigenetic, physiological, and environmental factors (10). The link between obesity and these associated comorbidities is, at least partly, the chronic low-grade inflammation that represents one of the hallmarks of obesity (11). Excepting a small subgroup of apparently metabolically healthy obese individuals, most obese patients develop chronic low-grade inflammation. This leads to metabolic and physiological perturbations that ultimately result in immunometabolic alterations in organs and tissues such as liver, brain, skeletal and cardiac muscle, blood vessels, lung, kidney, gut, and immune systems (12,13).

**2.1. Sources of inflammation**

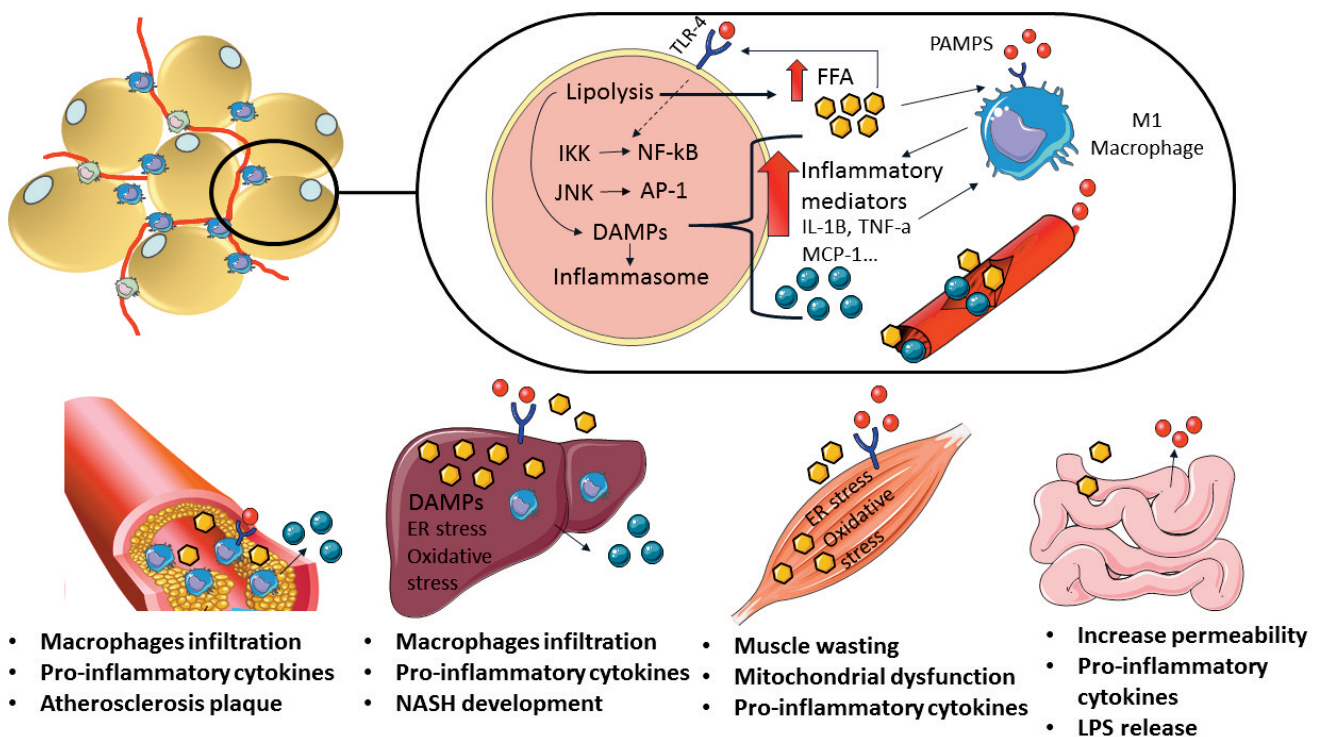
The low-grade systemic inflammation in obese subjects originates in visceral adipose tissue, caused by the hypertrophy of adipocytes and cellular stress signals. These signals dysregulate adipokine production, and increase the release of pro-inflammatory adipokines, cytokines, phase acute proteins, and chemokines (14) (Figure 1).

Over the past decade, adipose tissue has been studied as an active metabolic and endocrine organ that mainly regulates energy expenditure and glucose homeostasis through adipokine production. It is a complex organ, composed of adipocytes, fibroblasts, endothelial cells, and a wide-range of immune cells, giving it an important immune-modulator function (15).

Adiponectin and several other cytokines are released by lean adipose tissue. These adipokines play a role in maintaining an anti-inflammatory status. Adiponectin induces interleukin (IL)-10 and IL-1ra in macrophages, together with polarization of alternatively-activated macrophages (M2) (16). Moreover, the adipokines mitigate the production of the pro-inflammatory cytokines in adipocytes and macrophages stimulated by lipopolysaccharide (LPS) (17,18). Furthermore, lean adipocytes release anti-inflammatory cytokines IL-4, IL-5, IL-10, IL-1ra, IL-13, and IL-33, recruiting and polarizing infiltrated immune cells to an anti-inflammatory phenotype (19,20).

The increase in energy intake (usually the result of a high-fat diet) and decrease in energy expenditure (usually the result of a sedentary lifestyle) leads to a positive energy balance and fat accumulation in the adipocytes, which is caused by the dysregulation of the lipolysis/lipogenesis ratio (21). This hypertrophy of the adipose tissue plays a key role in the development of obesity-induced local inflammation (10).

Hypertrophic adipocytes activate stress-sensing pathways in response to metabolic and oxidative stress, increasing the phosphorylation of intracellular kinases as p38MAPK, Jun N-terminal kinase (JNK), and inhibitory-κB kinase (IKK) (22). Adipocyte size and p38MAPK, as well as JNK phosphorylation in the visceral fat of obese humans have been positively correlated with adipose tissue inflammation and whole-body insulin resistance (23,24). JNK and IKK phosphorylation activates activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB) transcription factors (25). This increases the gene expression of many pro-inflammatory cytokines. The NLRP3 inflammasome also plays a key role in adipocyte-hypertro-



**Figure 1:** Overview about how obesity induces local and systemic inflammation and its manifestations in blood, liver, muscle, and gut. (PAMPs = pathogen-associated molecular patterns, FFAs= free fatty acids, IKK = inhibitor of κ kinase; JNK: c-Jun N-terminal kinase; TLR4 = Toll-like receptor-4, AP-1: activator protein-1, NF-κB= nuclear factor kappa B, LPS= lipopolysaccharide)

phy-induced inflammation. It is activated in response to intracellular danger-associated molecular patterns (DAMPs), such as adenosine triphosphate (ATP), uric acid, an accumulation of palmitate, and advanced glycation end-products, which are all known to be increased in obesity (26) (Figure 1).

After this signal processing, fat adipocytes increase the production of pro-inflammatory cytokines, as monocyte chemoattractant protein (MCP)-1, IL-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$ . This is accompanied by a reduction of adiponectin and other anti-inflammatory cytokines. Thus, an imbalance of the inflammatory mediators results that is tilted toward a pro-inflammatory response, recruiting and polarizing immune cells to a pro-inflammatory phenotype.

## 2.2. Local and systemic effects

Adipocytes express surface stress ligands that are recognized by natural killer (NK) cells. The activation of NK cells leads to higher production of interferon-gamma (IFN- $\gamma$ ), which is essential for polarizing macrophages towards a pro-inflammatory phenotype (M1) (18). Macrophages represent up to 60% of all immune cells in the vascular stromal portion of adipose tissue (27). Adipose tissue macrophages are the major players in pro-inflammatory cytokine production in obese adipose tissue (28,29). It was previously postulated that all adipose tissue macrophages were driven by circulating monocytes, which infiltrate and differentiate to macrophages. However, in 2014, Amano and collaborators showed that macrophages from visceral adipose tissue were able to proliferate during obesity, and monocyte depletion had no significant impact on the number of adipose tissue macrophages (30). They also elucidated that macrophage proliferation was MCP-1 dependent. Interestingly, these adipose tissue macrophages express the molecule CD11c, which is mainly known to be expressed by dendritic cells. Wouters and his group (31) found a positive correlation between CD11c<sup>+</sup> adipose tissue macrophages from visceral depots and classical monocytes numbers in the circulation, suggesting that the classic macrophages originating from monocytes may also play a role in this obesity-induced adipose tissue macrophage phenotype.

CD11c<sup>+</sup> adipose tissue macrophage cells play a key role in the development of insulin resistance. Depleting these cells from obese mice can restore insulin sensitivity and decrease local and systemic pro-inflammatory cytokine production (32). Moreover, recent findings indicate that numbers of CD11c<sup>+</sup> adipose tissue macrophages from visceral depots are directly correlated with non-alcoholic steatohepatitis (NASH) development. These cells appear to induce macrophage and neutrophil accumulation in the liver (33).

CD11c<sup>+</sup> adipose tissue macrophages accumulate in visceral adipose tissue during obesity, forming crown-like structures (CLS) and producing great amounts of pro-inflammatory cytokines. They are therefore important contributors to the metabolic syndrome development. Toll-like receptor 4 (TLR-4) has been proposed to play a key role in this process. TLRs recognize pathogen-associated molecular patterns (PAMPs) and DAMPs, and induce a downstream signaling to activate NF- $\kappa$ B (34), and then induce pro-inflammatory cytokine transcription. Furthermore, TLR-4 seems to have a direct impact

on obesity-induced accumulation of CD11c<sup>+</sup> adipose tissue macrophages and adipose tissue pathology. Knockout mice for TLR-4 showed low activation of CD11c<sup>+</sup> adipose tissue macrophages after a high-fat diet, followed by a decrease in adipose tissue fibrosis (35). Moreover, wild-type mice injected with bone marrow from TLR-4 <sup>-/-</sup> mice presented low adiposity, improved glucose tolerance, and reduced accumulation of CD11c<sup>+</sup> adipose tissue macrophages in visceral adipose tissue (36). This suggests that the expression of TLR-4 in myeloid cells is necessary for monocyte recruitment and CD11c<sup>+</sup> adipose tissue macrophage accumulation. In addition, both TLR-4 and MyD88 full body knockout mice showed the same adipocyte hypertrophy as wild-type animals, however they exhibited much lower CD11c<sup>+</sup> adipose tissue macrophage percentages, crown-like structure formations and fibrosis (36), indicating that the TLR-4/MyD88 pathway is necessary for obesity-induced adipose tissue pathology.

During the past few years, it was established that saturated fatty acids (especially palmitate) could activate TLR-4 and then contribute to obesity-induced metabolic syndrome. Cameron Griffin and collaborators (2018) found that obese TLR-4 and MyD88 knockout mice generate fewer myeloid colonies compared to wild-type mice (36). These animals also failed to develop a palmitate or LPS-induced myeloid colony formation. Increased numbers of myeloid progenitors are observed in high fat diet-induced obesity and inflammatory macrophages mostly originate from these progenitors (37). In addition, TLR-4 expression in myeloid cells are necessary for insulin resistance and adipose tissue inflammation during obesity (38). These findings suggest that TLR-4 is required for diet-induced inflammation.

Other work has shown that TLR-4 knockout mice are protected from saturated fatty acid-induced inflammation (39,40). In this regard, Lancaster's group (41) identified that saturated fatty acids are not TLR-4 agonists, they are not able to form a TLR-4/MD-2 dimer and induce its downstream signaling. They also found a protection from saturated fatty acid-induced inflammation in those mice who lack TLR-4 (41). Finally, they discovered that saturated fatty acids cannot bind directly to TLR-4, but they play a secondary role in activating inflammatory signaling after an initial TLR4-dependent priming signal.

One of the most effective ways to activate TLR-4 signaling is through LPS stimulation. LPS is present at the membrane of gram-negative bacteria and is increased in the circulation during obesity. Intestinal permeability plays an important role in obesity-induced endotoxaemia. Many studies have reported a positive correlation between dietary fat consumption and plasma LPS concentration (42). Moreover, a recent investigation with non-obese and obese patients revealed that obese people had higher levels of markers for altered gastrointestinal barrier function in the serum, and showed a positive correlation between intestinal permeability and inflammatory markers (43). In addition, when the jejunum samples were challenge with lipids, both obese and non-obese samples presented increased intestinal permeability. However, samples obtained from the obese group had a 2-fold higher increase in permeability than the non-obese group, and took much longer to

restore the barrier function. Putting this all together, these data demonstrate that acute fat ingestion directly influences intestinal permeability, and chronic fat consumption may play a role in increasing intestinal and systemic inflammation (43).

### 2.3. Effect of obesity on other organs and tissues

Free fatty acids are toxic for several organs. The first step in the metabolism of lipids after digestion and absorption is regulated by the liver. Thus, nonalcoholic fatty liver disease (NAFLD) has reached alarming proportion in contemporary society (44). The trigger of NAFLD is the accumulation of triacylglycerol in hepatic parenchyma due to an imbalance between fatty oxidation and fatty storage (45). Interestingly, these two opposite pathways are regulated by the family of peroxisome proliferator-activated receptors (PPARs) (46). NAFLD can progress to NASH, cirrhosis, and hepatocellular carcinoma. This progression is dependent on hepatic inflammation, which is caused by Kupffer cells and an enhanced inflammatory response of hepatocytes (47). Furthermore, Ogawa et al (2018) showed that the increase in gut-derived endotoxin is necessary for the progression of NAFLD by inducing fibrosis and immune cells recruitment (48).

Excess fatty acid accumulation in hepatocytes leads to intracellular stress, (oxidative and endoplasmic reticulum (ER) stress) inducing cell apoptosis (49). This internal signaling, associated with extracellular-induced TLR-4 activation by LPS, leads to a chronic and harmful inflammatory signal (50) (Figure 1). In NAFLD, the classical pro-inflammatory cytokines are increased (TNF- $\alpha$ , IL-6 and IL-1 $\beta$ ), with an elevation of monocyte infiltration in the liver and macrophage differentiation to the M1 subset (i.e., higher expressions of CD11c, CD86) (51). The progression of NAFLD to NASH is characterized by the exacerbation of chronic inflammation and fibrosis, increasing fatty acid synthase (FAS), death receptor 5 (TRAILR-2), and TNF receptors, and a consequent increase in cytotoxic T lymphocytes (51).

In endothelial cells, higher levels of circulating free fatty acids, especially palmitate, induce a decrease in nitric oxide production, and increase the inflammatory response stimulated by LPS (52). The stressed endothelial cells increase the synthesis of integrins and selectins, thereby promoting immune cell infiltration in the vascular wall (53). Thus, monocytes and lymphocytes that have infiltrated into the vascular wall potentiate the inflammatory response, releasing pro-inflammatory cytokines (IL-1, TNF and IL-6) and chemokines (RANTES, IL-8 and MCP-1). The atherosclerotic plaque formation occurs when monocytes-derived macrophages phagocytize the lipid particles and induce foam cells (54) (Figure 1).

Skeletal muscle is a very important tissue for the maintenance of metabolic homeostasis. Elevated consumption of high-fat foods also induces lipid storage in the muscle, which increases diacylglycerol and ceramide accumulation inside myocytes (55). Both responses are related to increased cellular stress, observed by ER stress, together with enhanced unfolded protein response and mitochondria dysfunction, in turn causing oxidative stress (56). Additionally, the PAMPs and DAMPs that arise from lipid overload in obesity activate the TLR-4

pathway, triggering MAPK and NF- $\kappa$ B pathways (57). Pro-inflammatory cytokines and chemokines (MCP-1, IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ) are produced and released into circulation, leading to autocrine, paracrine, and endocrine effects (58) (Figure 1).

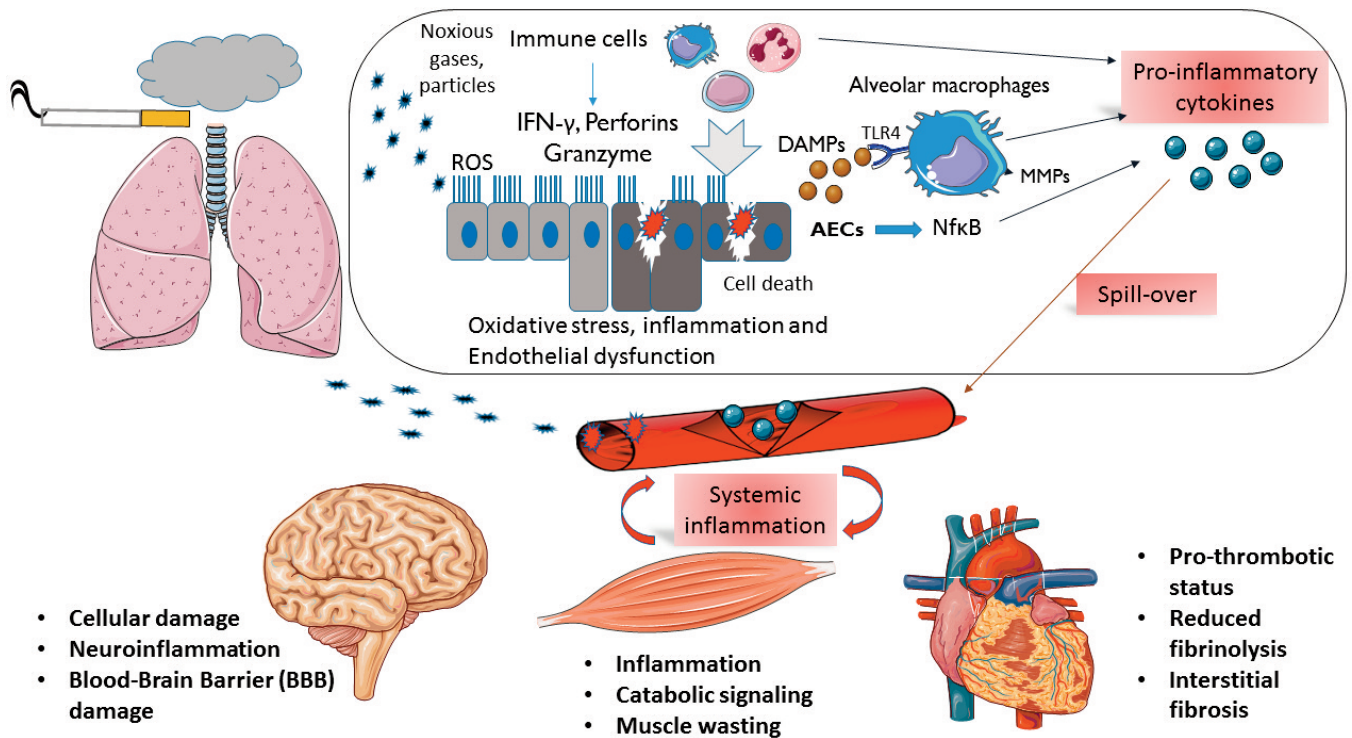
## 3. CIGARETTE SMOKE AS A BURDEN OF INFLAMMATION AND DISEASE

Tobacco smoking is a significant cause of morbidity and mortality, with approximately 5 million deaths caused by direct tobacco use and more than 600,000 deaths due to passive smoking worldwide every year. While in many countries intensified tobacco control efforts have resulted in a reduced prevalence of smoking, in other countries the number of smokers is steadily increasing. Cigarette smoking represents an important risk factor for cardiac infarction, stroke, and is the central risk factor for the development of bronchial carcinoma, COPD, and smoking associated lung fibrosis. Smoke associated diseases, such as COPD, are today classified as systemic inflammatory diseases because sustained inflammatory processes seem to be main drivers of co-morbidities, such as muscle wasting, vascular diseases, heart diseases, and stroke (59,60).

### 3.1. Sources and origins of inflammation

Cigarette smoke contains a multitude of immunomodulatory chemicals and gases, making it complex to discern a clear origin of the associated inflammation. However, it is suggested that the repeated contact of airway cells with specific noxious gases and particles leads to repetitive stress signals and inflammatory insults that are followed in the long-term by a chronic and progressive activation of the immune system (61). Accordingly, inflammatory processes originate in the pulmonary system, where the regular contact with toxic substances disturb the barrier function of the respiratory epithelium. Studies that have analyzed the bronchoalveolar lavage fluid (BAL) or and breath condensate of acute or chronic smokers proved that oxidative stress is an important factor for tissue damage. This is indicated by an accumulation of products of lipid peroxidation and extracellular matrix proteins (62,63). Airway epithelial cells, which represent a first line of defense against inhaled toxicants, are an important inducer of these inflammatory processes. In smokers, airway epithelial cells show characteristics of cellular damage, followed by the release of DAMPs. These molecules act in a paracrine fashion by activating pattern recognition receptors, such as TLR4, expressed by airway epithelial cells and other cells in the pulmonary system. In addition, the inhalation of smoke particles might also directly activate pattern recognition receptors (64). Consequently, TLR4 expression is significantly upregulated on airway cells of smokers (Figure 2).

In response to TLR4 activation, a role for heat shock protein 70 (HSP70), a known TLR4 agonist, has been shown, which is induced in airways upon smoke exposure followed by the activation of the innate immune system through TLR4/MyD88. Subsequently, NF- $\kappa$ B is translocated into the nucleus, inducing the secretion of a variety of pro-inflammatory cytokines. Cigarette smoke exposure has also been shown to induce ER stress in airway epithelial cells and



**Figures 2:** Illustration about cigarette-induced induction of oxidative stress and inflammation in airway epithelial cells (AECs) and the characteristics of extrapulmonary manifestations of inflammatory signals from the pulmonary system to brain, muscle, and cardiac tissue (TLR4 = Toll-like receptor-4, DAMPs= damage-associated molecular patterns, MMP=matrix metalloproteases, ROS= reactive oxygen species).

mouse lungs, which is suggested to amplify the inflammatory processes (65). Similarly, excessive activation of the inflammasome has also been shown to play a critical role in the innate immune response against cigarette smoke-induced noxious stimuli in the lung tissue (66). Consequently, increased levels of various cytokines (such as IL-1 $\beta$ , IL-6, IL-8, MCP-1), macrophage inflammatory protein (MIP) 1 $\alpha$ , regulated on activation normal T-cell expressed and secreted (RANTES), TNF- $\alpha$ , IL-12(p40), and IL-17 can be found in the BAL of long-term smokers (67). In addition, extracellular signal-regulated kinase signaling and increased p38MAPK in airway epithelial cells induces the expression of a variety of metalloproteases (MMPs), such as MMP9 and MMP12, and surfactant protein D, which can be also found in higher quantities in the lungs of long-term smokers (68,69) (Figure 2).

Cell damage, DAMP release, and the expression of chemokines are all triggers of immune cell invasion into the pulmonary system. Consequently, tissue resident or circulating macrophages, neutrophils, dendritic cells, and lymphocytes are activated and infiltrate the alveolar tissue. In particular, alveolar macrophages play a key role in the progression of lung inflammation by producing cytokines and various MMPs, such as MMP-1, MMP-2, MMP-9, MMP-12, and MMP-14 (68,70). CD4<sup>+</sup> and CD8<sup>+</sup> T cells increase dramatically in the lungs of long-term smokers. Shifting toward a type 1 profile, these cells produces large amounts of IFN- $\gamma$ , and release perforins and granzyme. In response to the massive accumulation of leukocytes, various inflammatory cytokines, such as IL-1 $\alpha$ , IL-5, IL-6, and IL-18, as well as the chemokine monocyte chemoattractant protein-1 and -3,

macrophage inflammatory protein-1 $\alpha$ , MIP-1 $\beta$ , MIP-1 $\gamma$ , MIP-2, MIP-3 $\beta$ , macrophage defined chemokine, granulocyte chemotactic protein-2, and interferon- $\gamma$ -inducible protein-10 are increased in lung tissue of smoke-exposed mice (69,71). As a response, the accumulation of FoxP3 T regulatory cells in lungs is suggested to be a countermeasure to control the inflammation. Beside this direct disturbance of the pulmonary immune equilibrium, cell damage and the chronically activated immune system lead to a compromised immune status that is amplified by an increased mucosal permeability (69). Consequently, opportunistic pathogens cause infections in smokers, forcing inflammatory processes. In the long run, cellular damage leads to small airway remodeling in long-term smokers, which is characterized by mucus cell hyperplasia and peribronchiolar fibrosis, as well as increased airway smooth muscle mass (72).

Regarding the systemic inflammation of long-term cigarette smokers, it is hypothesized that these primarily local inflammatory processes in the pulmonary system tend to spill-over into the systemic circulation that serves as a mode of transit for inflammatory signals throughout the body. Thus, inflammation is suggested to be the main driver of pathophysiologic and degenerative processes in other tissues (Figure 2). In addition, smoke pollutants have been shown to directly cross through the alveolus-capillary interface. The particulate phase of cigarette smoke contains various lipophilic components, which are able to pass the lipid bilayer of the respiratory membranes, and therefore spread through the systemic bloodstream. Hence, these particles directly target specific organs where they might be recognized by receptors of the innate

immune system that initiate inflammatory signaling cascades through NF- $\kappa$ B activation (63,73).

### 3.2. Systemic inflammation during cigarette smoking

Acute cigarette smoking is followed by a temporary increase of systemic markers of oxidative stress, inflammation, and thrombosis, indicated by increased thiobarbituric acid reactive substances (TBARS), neutrophil elastase, leukotrienes, and leukocytes. In long-term smokers, these acute inflammatory processes induce tissue damage and turn into chronic inflammatory processes. (74,75). Lymphocytes turn into an activated phenotype indicated by an elevated expression of adhesion molecules, such as ICAM-1, VCAM-1, and E-selectin, which mediate the migration into the bronchoalveolar system or other tissues (76). These molecules can also be found in elevated quantities in their soluble form in heavy smokers (71). Regarding cytokines, the smoke-induced systemic low-grade inflammation is characterized by chronically elevated levels of markers for inflammation, tissue deterioration, and coagulation, such as C-reactive protein (CRP), TNF- $\alpha$ , von Willebrand factor, tissue inhibitor of metalloproteinases 1 (TIMP-1), factor VII, and fibrinogen (77).

The chronic enhancement of inflammation and oxidative stress in the blood, as well as some soluble components of cigarette smoke, disturb the function of endothelial cells. On the one hand, chronic inflammatory signals reduce nitric oxide (NO) production and vascular compliance, and are followed by aberrant interactions between endothelial and immune cells resulting from an increased expression of adhesion molecules. On the other hand, free radical formation from components of cigarette smoke and the activation of endogenous sources of free radicals such as uncoupled NOS, xanthine oxidase, and NADPH oxidase, further decrease NO availability, increasing coagulative factors and lipid peroxidation (75). Oxidative stress and inflammation are primary inducers of endothelial dysfunction, which represents an early hallmark in the development of atherosclerosis. Hence, after long-term smoking, dysfunctional endothelial cells express lower levels of prostacyclin, thrombomodulin, and tissue plasminogen activator (tPA), while expression levels of endothelin-1, angiotensin II, plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor (vWF) are increased (70,78).

In vitro studies proved that cigarette smoke also induces apoptosis, autophagic cell death, and necrosis in endothelial cells. In this regard, cigarette smoking decreases p53 and Bcl-2 expression, disrupts the vascular endothelial growth factor (VEGF) and fluid shear stress-mediated VEGFR2/phosphoinositide 3-kinase (PI3K) signaling pathway, and reduces the cytochrome-c oxidase II expression through aberrant DNA methylation. Further vascular damage induced by excessive apoptosis was also shown to be initiated by a p53-independent caspase-3 activating pathways and protein carbonylation, which is caused by reactive oxygen species in cigarette smoking (79–81).

### 3.3. Effects of smoking on other organs and tissues

Toxic effects of cigarette smoke on the myocardium have been proven experimentally as well as clinically. It was

demonstrated that smoking promotes neutrophil infiltration in the myocardium, alters T cell function, and causes DNA adducts in the myocardium (82) (Figure 2). Due to increased oxidative stress, ROS-sensitive signal transduction pathways (such as MAPKs) and various transcription factors (including NF- $\kappa$ B), are activated. This results in an aberrant cytokine profile (83,84). Gene analysis of the hearts of mice revealed an upregulation of the xenobiotic-metabolizing enzyme cytochrome P-450 1A1, and a downregulation of PAI-1, representing a key gene involved in fibrinolysis. These inflammatory processes are suggested to increase the risk for several diseases of the cardiovascular system in human smokers as well (85,86).

The muscles of smoke-exposed mice exhibited an increased expression of inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$  (73). Furthermore, chronic exposure to cigarette smoke reduces muscle capillary-to-fiber ratio (76). Oxidative stress and inflammatory signals have been shown to activate the ubiquitin proteasome system, inhibit mitochondrial biogenesis, and reduce activation of the anabolic signaling pathways, such as the protein kinase B (Akt) and rapamycin (mTOR) pathways. Consequently, protein balance turns towards an enhanced degradation leading to muscle wasting, a reduced percentage of type I fiber, a lower muscle fiber cross-sectional area, and decreased muscle oxidative activity (73,87).

With regard to oxidative stress and inflammation, atherosclerosis and vascular brain lesions share similar pathological features (Figure 2). Accordingly, a higher expression of VEGF, ICAM-1, IL-8, and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) was also observed in cultured brain endothelial cells in response to smoke exposure (88). Cigarette smoke extracts induced heme oxygenase-1 (HO-1) expression mediated by the phosphatidolcholine phospholipase C (PC-PLC)/protein kinase C $\delta$  (PKC $\delta$ )/NADPH oxidase-dependent pathway and the platelet-derived growth factor receptor (PDGFR)/PI3K/Akt pathway (70). In rat brains exposed to cigarette smoke, endothelin-1 levels decreased, which is suggested an effect on hemodynamic responses (89). Since oxidative stress is known to play an important role in the pathogenesis of ischemic brain injury, cigarette smoking is associated with various cerebrovascular-related diseases, in particular, smoking is a risk factor for stroke (90).

Moreover, cigarette smoke negatively affected endothelial tight junctions, which was proved in animal experiments, and negatively affects the viability of the blood-brain-barrier. Smoke-induced neuroinflammation was confirmed by various in vivo studies using mouse and rat models. Mice exposed to cigarette smoke showed higher levels of ROS, induction of lipid peroxidation, activation of the transcription factors NF- $\kappa$ B and AP-1, as well as activation of MAPK, including JNK, ERK, p38, and COX -2 in various regions of the brain (90). In parallel, cigarette smoke altered enzymatic antioxidant defenses by reducing superoxide dismutase (SOD) as well as catalase and increasing glutathione S-transferase (GST) activity in rat brains. These alterations favor the proteolytic degradation of  $\alpha$ II-spectrin through caspase-3 and the dephosphorylation of phosphoproteins enriched in astrocytes-15 (PEA-15), both indicating apoptotic cell death (91).

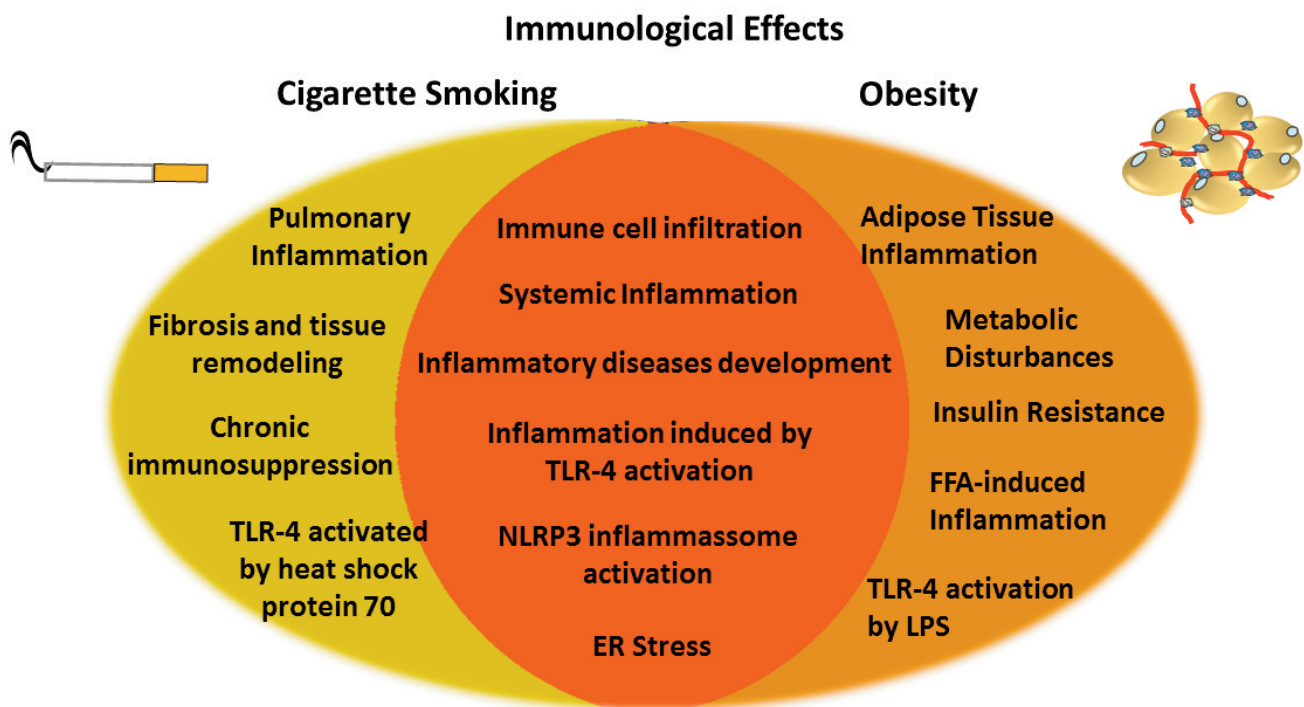
#### 4. DIFFERENCES IN SMOKE-INDUCED INFLAMMATION AND INFLAMMATION DURING OBESITY

Both cigarette smoke and obesity-induced inflammation initiate a local inflammatory response, culminating in the recruitment of immune cells to the tissue in a feedback response trying to decrease this initial inflammation and avoid an exacerbation (77,92). While the source of inflammation in obese subjects seems to mainly be the visceral adipose tissue, inflammation after cigarette smoking originates in the pulmonary system. Accordingly, both inflammatory conditions represent risk factors for partly overlapping sets of diseases such as cardiovascular diseases, rheumatoid arthritis, hypertension, muscle wasting, and depressive disorders. However, there is a difference in other specific comorbidities (Figure 3). Regarding lung cancer, the proportion of cases attributable to smoking is estimated to about 90 percent in countries with a history of tobacco smoking. Similarly, smoking accounts for at least eight of ten COPD-related deaths (93), and the prevalence of tobacco use in idiopathic pulmonary fibrosis (IPF) is estimated in ranges from 41-83% (94). However, there are several other smoke-related diseases, such as coronary heart disease (CHD) or stroke, which at least partly progress due to the distribution of small particles and noxious gases throughout the body, directly triggering inflammatory processes. In contrast, obesity represents a specific risk factor for dyslipidemia, diabetes mellitus type II, various liver diseases (such as NAFLD), and certain cancers (such as colorectal and prostate cancer in men and endometrial, breast, and gallbladder cancer in women). However, both inflammatory conditions (i.e., obesity and long-term cigarette smoking) are characterized by a vicious cycle of local signals of cellular stress, inflammation, progressive immune cell infiltration, and the

release of inflammatory cytokines and chemokines, leading to a spill-over into the circulation system. Subsequently, inflammatory processes target other tissues, which might account for various comorbidities. Obese smokers who combine both inflammatory disorders have been shown to have increased morbidity and mortality (73,92).

In the long-run, both obesity-induced inflammation and cigarette smoke-induced inflammation, are suggested to impair immune competence against invading pathogens. This condition of chronic immunosuppression seems to be much more pronounced in smokers due to significant impairment of the pulmonary barrier function (95). In obese patients, Neidich and collaborators (96) reported an increased risk of influenza among vaccinated adults who are obese, suggesting dysfunctional immunity. For both inflammatory conditions, it is suggested that chronic immune activation is a driver of immunosenescence. Accordingly, systemic inflammation was demonstrated to be a key element of the immune risk profile during aging, because chronic activation promotes the accumulation of senescent T cells that show a reduced reactivity against new invading pathogens (97).

While the pathogenesis of both inflammatory disorders have several features in common, there are also distinct differences in their development, extent, and the progression of immune activation (Figure 3). During cigarette smoking, the chronic exposure to toxic substances and inhaled particles seem to be important effectors of oxidative stress (75). Resulting severe cellular damage affects the function and integrity of airway epithelial cells (63). Subsequently, an important concomitant effect of cigarette smoke-induced inflammation is the significant increase of proteolytic peptidases, such as MMPs, which



**Figure 3:** Specific inflammatory characteristics of cigarette smoke-induced inflammation (left), obesity-associated inflammation (right), and inflammatory characteristics both have in common (middle).

indicate progressive tissue deterioration and degradation. The resulting repair and remodeling processes induce fibrosis and the formation of excess fibrous connective tissue (68,69). Obesity is also accompanied by fibrotic process that occur in subcutaneous adipose tissue. The increase in collagen and extracellular matrix components induce an early insulin resistance and worsen the inflammation and cellular stress by reducing the adipocytes hypertrophy capacity (98). Adipose tissue fibrosis is strongly correlated with other obesity-associated comorbidities. Higher levels of fibrosis are found in a genetic model of lipodystrophy. These mice showed the same imbalance regarding insulin sensitivity, inflammation, and macrophage infiltration as found in obesity (99).

Another important feature of cigarette smoking is an enhanced platelet reactivity and increased blood coagulation, indicating an increased risk for thrombosis, peripheral artery occlusive disease (PAOD), and cardiovascular diseases (100). Since inflammatory processes in COPD patients often progress even after the cessation of smoking, and a combined accumulation of Th17 cells is observed in such cases, there are ongoing discussions concerning autoimmunity processes as potential drivers of disease progression in these cases (101).

An additional salient dissimilarity between cigarette smoking and obesity is that obesity is primarily characterized by metabolic disturbances. The greater accumulation of fatty acids within adipocytes changes the cell metabolic profile, increasing lipolysis and free fatty acids, which activate stress signals, inflammatory processes, and the production of inflammatory mediators by metabolic cells with secondary chemoattraction of immune cell infiltration (102).

An important pathway involved in this process is TLR4 signaling, since it is strongly activated by LPS and is required for free fatty acid-induced inflammation, which are both increased in obese subjects. The NLRP3 inflammasome also plays an important role in obesity-induced inflammation. Both TLR4, as well as NLRP3, can impair mitochondrial function in white adipose tissue adipocytes (103) and increase pro-inflammatory cytokine release. TLR4 activation in immune cells drives the cells to a pro-inflammatory phenotype exacerbating the tissue inflammation. Moreover, in the cross-talk between adipocytes and infiltrating immune cells, TLR4 upregulates MMP-1 expression in adipose tissue by increasing its expression in immune cells. This may contribute to the pathogenesis of obesity-induced inflammation (104). Similarly, cigarette smoke condensate has been shown to induce a macrophage pro-inflammatory response *in vitro*, which was dependent on MyD88, IL-1R1, and TLR4 signaling (105). In contrast to obesity, this pathway is not attributable to LPS. Instead, heat shock protein 70, which is also a TLR4 agonist, induces immune processes in the airways upon smoke exposure, which probably activates the innate immune system through TLR4/MyD88, resulting in airway inflammation (105).

Regarding molecular signaling, both smoke- and obesity-induced inflammation involve increased ER stress, followed by the activation of the innate immune response, which main-

ly affects adipocytes during obesity and airway epithelial cells in smokers (65,106). Similarly, both conditions are characterized by the activation of the NLRP3 inflammasome that is suggested to be an important driver of the pathogenesis of the specific diseases (66).

## 5. ANTI-INFLAMMATORY EFFECTS OF EXERCISE

It is well established that an active lifestyle can mitigate or counter the development of many metabolic and inflammatory diseases. For both obese patients and patients with pulmonary diseases, exercise training is an effective non-pharmacological treatment strategy. Exercise therapy increases strength, endurance capacity, and various quality of life scores. Recent studies provided evidence that regular and moderate exercise exerts protective effects due to its immunoregulating properties. In this regard, observational and interventional studies have shown that regular exercise training is able to reduce circulating inflammatory markers in healthy and diseased individuals (107). Due to the differences in the inflammatory pathogenesis of both diseases, the immune-regulating effects of exercise may differ between them. These differences might at least have implications for the type, impact, and success of exercise as a treatment strategy for these chronic inflammatory diseases.

**5.1. Immune-regulatory effects of exercise during obesity**  
Since obesity is a metabolic disease caused by exacerbated fat accumulation, alterations in metabolic pathways, and activation of inflammatory pathways, strategies to increase fat oxidation, restore metabolism homeostasis, and decrease inflammation have achieved success in obesity treatment.

Several studies, in humans and rodents, provide evidence that regular exercise can decrease fat mass accumulation (77), even after high fat-diet feeding. The exercise-induced loss of body fat is associated with the improvement of many obesity-related disorders, such as insulin resistance, cardiovascular disease, and NASH (46).

The metabolic improvement in obese subjects resulting from exercise could be explained on the one hand by increases in fatty acid mobilization in adipose tissue, leading to a reduction in cellular stress. These fatty acids are, therefore, oxidized by skeletal muscle to produce energy, which decreases the “toxic” free fatty acids in circulation.

Exercise training has also been shown to reduce adipose tissue inflammation. Three months of an aerobic exercise program decreased IL-6 and TNF- $\alpha$  protein expression in the subcutaneous adipose tissue of diabetic and non-diabetic obese patients (108). The main mechanisms behind this anti-inflammatory role of exercise include a reduction in immune cell infiltration and a shift in the pro-inflammatory profile (found in obese adipose tissue) to an anti-inflammatory one (found in lean adipose tissue). Human studies have found that exercise training can decrease M1 markers in circulating monocytes and increase M2 expression. Eight weeks of low-intensity exercise training was sufficient to increase CD14 and AMAC-1 (M2 markers) gene expression and decrease CXCL2 in the



peripheral blood mononuclear cells of sedentary individuals (109). A short-term period (two weeks) of moderate-intensity continuous training reduced CCR2 and CXCR2 mRNA in circulating monocytes from obese adults, while high-intensity interval training increased CCR5 expression (110), suggesting that moderate exercise provides anti-inflammatory effects on monocytes.

Furthermore, the aerobic training is able to modify adaptive immune responses (111). The subsets of lymphocytes are altered by acute or chronic exercise, and these alterations depend on the intensity and duration of exercise, pre-exercise status of training and energetic substrate availability. Athletes who exercise at higher intensity and for long durations (e.g., marathoners, triathletes and cyclists) showed increased in Treg lymphocytes in the systemic circulation (112). Moreover, CD4<sup>+</sup> T cells positive to TGF- $\beta$  and IL-10 were increased in marathon runners (113).

In studies with animals, Kawanishi and collaborators (114) found that twelve weeks of treadmill exercise in obese mice reduced adipose tissue TNF- $\alpha$  and IL-6 gene expression, followed by a reduction in the percentage and the number of macrophages and CD8 T cells in the stromal vascular fraction (SVF). These macrophages also presented a decreased CD11c surface expression, which represents a marker of M1 macrophages (114). Similarly, four months of exercise training reduced adipose tissue inflammation, macrophage infiltration, and increased gene expression of CD163 – a marker for M2 macrophages (115). This suggests that exercise can decrease a macrophage inflammatory phenotype, as well as decrease macrophage infiltration, which restored the obesity-induced adipose tissue inflammation. In a recent paper, our group demonstrated that 8 weeks of treadmill training (60 min at 60% of maximal velocity, 5 days a week) was able to induce the M2 phenotype in macrophages from subcutaneous adipose tissue, even in those mice lacking PPAR $\gamma$  in the myeloid cell lineage (116). PPAR $\gamma$  is one of the main regulatory nuclear transcription factors for M2 cells. In this study, we also observed an increase in IL-10 production by stimulated peritoneal macrophages from trained mice (116). These findings indicate that exercise can induce an anti-inflammatory response in macrophages by mechanisms independent of PPAR $\gamma$ .

Studies on animals fed a high-fat diet showed that endurance exercise training decreased expression of TLR-4 in monocytes, adipose tissue, and bone-marrow-derived macrophages, followed by a reduced TLR-4/MyD88 interaction (117). Humans studies revealed that obese people submitted to an exercise program showed low levels of TLR-4 in peripheral-blood mononuclear cells (117). A short-term program (two weeks) of both intense and moderate exercise decreased TLR4 expression in the circulating leucocytes of sedentary adults (118).

Targeting TLR-4 is an important step to control NF- $\kappa$ B activation and pro-inflammatory cytokine transcription, which represents an important pathway for obesity-induced insulin resistance. Several studies have reported that different types of exercise can inhibit the activation of the NF- $\kappa$ B pathway,

followed by decreased inflammation and restored insulin signaling (119). Moreover, exercise training decreases endotoxaemia by improving gut barrier function (120). LPS is the most potent TLR-4 ligand, decreasing the LPS concentration in the serum implies an inhibition of TLR-4 signaling, thus decreasing NF- $\kappa$ B activation.

These alterations in immune cells induced by exercise can be, in part, modulated by muscle mass contraction. Pedersen and collaborators (121) showed that during exercise muscle mass increases the capacity to produce cytokines, indicating that muscle is an important immune-modulator organ. IL-6 is elevated in serum after an acute bout of aerobic exercise. Muscle-derived IL-6, together with IL-10 and IL-1ra expression by leukocytes, represent important anti-inflammatory cytokines that inhibit IL-1 and TNF- $\alpha$  signaling and improve insulin sensitivity. Moreover, IL-6 has been shown to enhance lipolysis and fatty acid oxidation in the muscle and adipose tissue, as well as increase glucose uptake in an AMPK-dependent manner (3).

IL-15, which is upregulated in the skeletal muscle of trained people (122), may also play a role in reducing fat mass. It reduced visceral fat in mice (123). Plasma levels of IL-15 are inversely correlated with visceral fat amount in obese people (123). Furthermore, IL-15 induces different NK and T cell subtype differentiation, and inhibits cell apoptosis (124,125).

## 5.2. Anti-inflammatory effects of exercise after smoke exposure

Despite the ever increasing number of patients suffering from smoke-induced diseases such as COPD, current treatments can only decelerate, not prevent, the progression of the diseases (126). Often, these patients are limited in their ability to perform exercises. However, after some weeks of exercise training, they benefit by improving their strength, cardiopulmonary fitness, and quality of life. In response to regular physical activity, some human and murine studies also proved immune-regulating effects. In humans, a reduction of systemic CRP and IL-6 levels in response to physical activity has been shown (127). In smoke-exposed mice, regular treadmill running was followed by lower levels of inflammatory, chemoattractive, and coagulative proteins in the blood (73). Regarding blood coagulation, a reduction of von Willebrand factor and Factor VII has been shown. Similarly, a reduced surface expression of adhesion molecules on circulating lymphocytes such as VCAM-1, ICAM-1 and CD62L, has been shown after regular treadmill running. In parallel, several inflammatory cytokines such as IL-1 $\alpha$ , MCP-3, MIP1 $\beta$ , MIP-1 $\alpha$ , and CD40L decreased after exercise in plasma. Exercise also decreased the rate of leucine appearance, suggesting an attenuation of accelerated whole-body protein breakdown in patients with COPD (128).

Physical training does not improve lung function in patients with COPD. Accordingly, increased cardiorespiratory fitness is mainly attributed to improvements of muscle and cardiac function. Animal studies suggest that regular exercise training is able to at least partly reduce lung inflammation and decelerate the remodeling of lung tissue. Indeed, exercise increased Th1 responses and suppressed Th2 cytokine levels in the

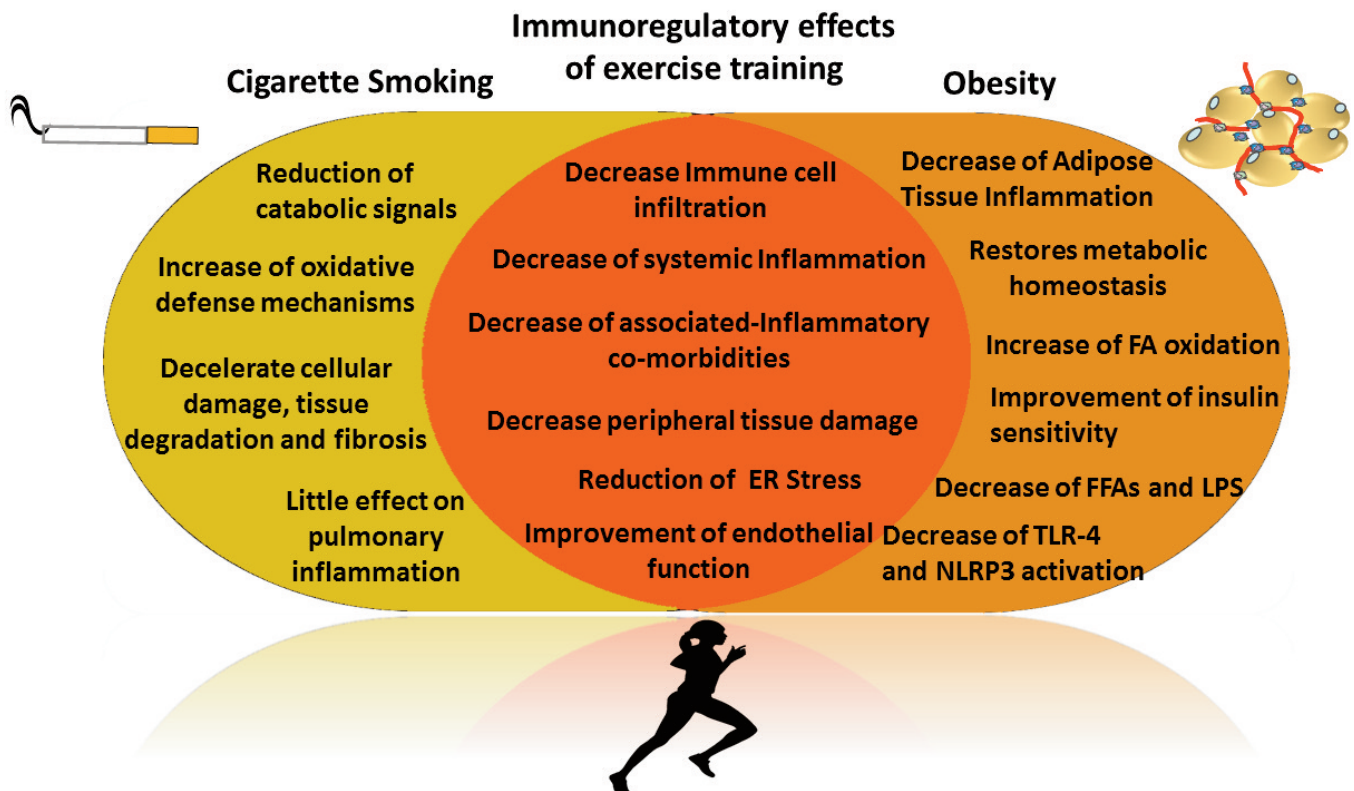
lungs of mice after smoke exposure (129). These immune-regulating effects might be due to an increased antioxidant defense after training, which was demonstrated by a reduction of oxidative stress markers (130). Prior exercise training has been shown to alleviate markers of lung inflammation and lung remodeling induced by subsequent exposure to environmental cigarette smoke. Accordingly, a significant reduction of inflammatory cell infiltration, cytokines, chemokines, adhesion molecules, activation of NF-κB was demonstrated, accompanied by a reduced bronchoalveolar-capillary permeability and epithelial thickening (131).

There are only limited data available about the effects of exercise on the endothelium in smokers. In mice it was shown that exercise is able to reverse peripheral endothelial dysfunction after smoke exposure by increasing maximal endothelium-dependent dilation. In parallel, protein expression of phosphorylated eNOS was increased in the aorta of trained mice (132). Endothelial dysfunction and cardiac dysfunction are strongly connected. Accordingly, it is assumed that the protective effects of exercise towards the endothelium might also be cardioprotective (133,134). Bowen et al. (132) proved that right ventricular dysfunction after smoke exposure can be reversed by exercise training, while the underlying mechanisms are not known. Exercise training has been shown to reverse various aspects of muscle wasting after long-term smoking. In the muscle of smoke-exposed mice, a decrease in inflammatory signals such as TNF-α and IL-1β on RNA level has been reported after training (73). The anti-inflammatory effects are suggested to involve blunting of the activation of catabolic pathways, such as the ubiquitin proteasome system. In this

context, exercise decreased FoxO1 phosphorylation, reduced the expression of atrogin-1 and MuRF-1, and abrogated the expression of protein catabolic E3 ligases in muscle, which are considered key factors in myofibrillar protein breakdown via the ubiquitin proteasome system. Similarly, exercise increases anabolic signaling after smoke exposure by increasing IGF-1 signaling and activation of the Akt-mTOR-pathway in muscle tissue. Exercise stimulates the metabolic capacities of muscles after smoke exposure. Thus, an increased expression of genes involved in fatty acid transport into the mitochondrial matrix and an increase of glucose uptake was observed in smoke exposed of mice after training (73).

### 6. DIFFERENTIAL IMMUNOLOGIC REGULATION OF EXERCISE DURING OBESITY AND AFTER SMOKE EXPOSURE

The impact of exercise training as a therapeutic strategy for obese patients excluded this patients or for patients with pulmonary diseases might at first be strongly dependent on the progression or pathologic stage of the disease. However, in the wide array of smoke-induced pulmonary diseases the effects of therapeutic training are limited. On the one hand, COPD patients at least patients in stage III or IV—are only able to take part in effective types of exercise training programs in a limited fashion (135). On the other hand, exercise has neither the potential to regenerate lung tissue nor to improve lung function significantly (129). Instead, regular exercise training mainly alters the function of peripheral tissues such as cardiac function or muscles. Some studies have



**Figure 4:** Specific effects of regular exercise training on cigarette smoke-induced inflammation (left side) and obesity associated inflammation (right side) and common effects (middle).

demonstrated muscular dysfunction, indicated by anabolic resistance, in response to training (136). However, this process might depend on the progress of the disease, because there is also some evidence for a reduction of inflammation and oxidative stress followed by increased activation of anabolic signals, decrease of catabolic pathways, strength, and endurance capacity (73). Regarding tissue degradation, it is suggested that the immune-regulating effects of exercise mainly decelerate or stabilize the level progression of cellular damage and fibrosis (73,92) (Figure 4).

During obesity, however, exercise appears to have a much more pronounced effect. Since obesity is characterized by strong metabolic alterations in adipose tissue and other organs, many pathways are involved in obesity-induced inflammation, thus exercise can act in different ways to restore body homeostasis and reduce inflammatory responses. Exercise training induces fatty acid oxidation, which reduces free fatty acids. Moreover, trained human and rodents presented lower LPS concentration in the serum (137,138). Combining these factors culminates in a decrease of TLR4 and NLRP3 activation, which reduces immune cell infiltration into the adipose tissue, inhibits the pro-inflammatory phenotype and decreases local and systemic inflammation (139). Furthermore, exercise can restore glucose homeostasis and insulin sensitivity in many different organs and tissues. Recent work reported that adipose-specific insulin resistance increases MCP-1 expression and M1 macrophage infiltration into the adipose tissue (140). Therefore, restoring insulin signaling is an important pathway to decreasing obesity-induced inflammation (Figure 4).

Several studies have reported that the effects of exercise on obesity are independent of an alterations in fat mass index or high-fat diet consumption (114,115,141). In many studies, there is no nutritional intervention; they only add exercise to the routine, and the effects include reduced inflammation, restored glucose and insulin signaling, and decreased obesity-associated comorbidities (46,141). So, many years of research in the obesity field lead us to believe that the problem facing Western society is not the high consumption of fat by itself, but the combination of this with a sedentary lifestyle (142,143). In contrast, smoke-induced inflammation develops independently of a sedentary lifestyle. There is no consistent association between physical inactivity and pulmonary function in adult smokers (144). Accordingly, regular smoking is suggested to represent an inflammatory trigger that cannot be completely compensated for by regular exercise. Consequently, smoking history and smoking cessation should be given special attention in prevention and therapeutic strategies.

## 7. CONCLUSION

Inflammation during obesity or after cigarette smoking has several aspects in common, but there are also distinct differences in their pathogenesis. Accordingly, it is reasonable to talk about an obesity-type of chronic low-grade inflammation and a cigarette smoke-type of systemic inflammation. Disease-specific severity, localization, and tissue-specific immunologic signaling pathways reflect some of the main differences between both inflammatory diseases. Downstream, smoking and obesity share some hallmarks of inflammation

that affect the risk for various inflammatory comorbidities, such as cardiovascular disease and rheumatoid arthritis (2). It is worth mentioning that there is a proportion of patients who combine obesity and smoking, and the interaction between both resulting inflammatory processes increases the overall risk for morbidity and mortality. Regarding the immune-regulating effects of exercise, it is important to note that exercise training represents a holistic therapeutic approach that affects both local as well as systemic inflammatory processes in obese patients and long-term cigarette smokers. However, in cases of advanced pulmonary damage after long-term cigarette smoking, the immunological effects of therapeutic exercise are limited, which makes it important to start therapeutic training as soon as possible.

Accordingly, exercise training represents an integrated therapeutic approach with only limited negative side effects (145). But due to the distinctive differences between obesity and cigarette smoking, future studies should consider investigating the immune-regulating exercise strategies that more specifically target disease-specific inflammation.

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