Metabolic syndrome, inflammation and atherothrombosis

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Summary

Extensive research of the past decades altered our traditional concept about the genesis of atherosclerosis fundamentally. Today, the crucial role of inflammation in the formation and progression of atherosclerotic plaques is indisputable. Patients at high risk for developing cardiovascular disease, owing to poor diet, obesity and low physical activity have been shown to exhibit a particular inflammatory pattern.

Therefore, the present review highlights the crosslink between the metabolic syndrome (MetS), adipose tissue, adipokines and selected inflammatory cytokines in the context of atherothrombosis and cardiovascular disease.

Zusammenfassung

Extensives wissenschaftliches Engagement der vergangenen Jahrzehnte hat unsere Sichtweise bzgl. der Entstehung von Atherosklerose grundlegend verändert. Heute ist allgemein anerkannt, dass Entzündung diesen Prozess maßgeblich beeinflusst. Insbesondere zeigte sich bei Patienten mit einem hohen Risiko für kardiovaskuläre Erkrankungen, bedingt durch mangelnde körperliche Betätigung, Übergewicht und Fehlernährung, ein individuelles Entzündungsmuster.

Dieser Artikel beleuchtet den Einfluss von Fettgewebe, Adipokinen und pro-inflammatorischen Zytokinen auf die Entstehung von kardiovaskulären Erkrankungen in Anbetracht des metabolischen Syndroms.

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Cardiovascular disease (CVD) is the leading cause of death in the western world, both in men and women, accounting for one of three deaths in the United States (US) today (1). In the mid 20th century the Framingham Heart Study subsequently revealed the epidemiology of atherosclerotic CVD, identifying smoking, obesity, glucose intolerance, high cholesterol levels and many more factors that substantially contribute to risk of cardiovascular death (2).

In 2011, 21% of men and 17% of women in the US older than 18 years of age reported to be current smokers and the proportion of non-smoking population exposed to second-hand smoke (detected by serum cotinine) declined from 53% in 1999–2000 to 40% in 2007–2008 (1). According to the National Health and Nutrition Examination the mean energy consumption among US adults increased by 22% in women and 10% in men between 1971 and 2004. Thus, forecasts predict an increase in the prevalence of obesity from 35% today to 51% by 2030 in US Americans (1, 3). Based on data between 2007 and 2010 in the adult US population older than 20 years of age,

- 33% were considered to be hypertensive,
- 14% had serum cholesterols levels greater than 240 mg/dl and
- >8% had diagnosed diabetes mellitus (1).

Currently, adjusted population attributable fractions for cardiovascular mortality are estimated to be

- 41% for high blood pressure,
- 14% for smoking,
- 13% for poor diet,
- 12% for insufficient physical activity,
- 9% for abnormal glucose levels (1).

However, there is a substantial overlap between these pathologies and it has therefore been suggested that the overall attributable risk for these risk factors is 50% (4). Given the considerable prevalence of CVD and the disappointing outlook, research has extensively focused on discovering the pathogenesis of atherosclerosis.

Today the key role of inflammation in the multiple manifestations of atherosclerosis is well-established. The present review highlights the crosslink between the metabolic syndrome (MetS), adipose tissue, adipokines and selected inflammatory cytokines in the context of atherothrombosis and CVD.

The metabolic syndrome

MetS is a cluster of risk factors for CVD, thus, the risk of developing CVD is approximately doubled in that population (5). The syndrome has received increased attention after practical and updated definitions by the Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF) (5–7). Although other

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Tab. 1 Common definitions of the metabolic syndrome

IDF (2005)	NCEP/ATP-III (2001–2005)	WHO (1998)
• waist circumference ≥102 cm (men), ≥88 cm (women) • plus 2 of: – blood pressure ≥130/85 mmHg or treatment – triglycerides ≥1.7 mmol/l (150 mg/dl) or treatment – HDL <1.0 (39 mg/dl) (men), <1.3 (50 mg/dl (women) – glucose 5.6 mmol/l (101 mg/dl) or treatment	at least 3 of the following: • waist circumference ≥102 cm (men), ≥88 cm (women) • blood pressure ≥130/85 mmHg or treatment • triglycerides ≥1.7 mmol/l (150 mg/dl) or treatment • HDL <1.0 (39 mg/dl) (men), <1.3 (50 mg/dl (women) • glucose 5.6 mmol/l (101 mg/dl) or treatment	• insulin resistance or diabetes or impaired glucose tolerance or impaired fasting glucose • plus 2 of: – body mass index ≥30 kg/m² or hip/waist ratio >0.9 (men) / >0.85 (women) – blood pressure ≥140/90 mmHg or treatment – triglycerides ≥1.7 mmol/l (150 mg/dl) or treatment – HDL <0.9 (35 mg/dl) (men), <1.0 (39 mg/dl) (women) – glucose 5.6 mmol/l (101 mg/dl) or treatment – microalbuminurea

classifications exist, and the criteria vary to some degree, all definitions identify a population with increased risk for developing type 2 diabetes mellitus and CVD (8–11). The definition for MetS by the adult treatment panel (ATP) III criteria of the national cholesterol education program (NCEP) includes a cluster of five factors: An increased waist line, elevated triglycerides (TG), elevated fasting plasma glucose (FPG), high systolic blood pressure, and low levels of high density lipoprotein (HDL) cholesterol. Three or more of these components define the presence of MetS (11, 12).

Whereas the original definition by Reaven (1988) (13), as well as the definition by the World Health Organisation (1998) emphasised insulin resistance as mandatory for the diagnosis, no measure of insulin resistance is present in the updated definitions by IDF and ATP-III (2005) (▶Tab. 1) (14). Instead, the role of central obesity measured by waist circumference has been given more attention, and is mandatory by the IDF criteria. A few comparative studies have aimed to compare the various definitions, and it seems that the IDF-definition identifies slightly more individuals with the syndrome (15–17).

As all the individual components of the syndrome have been shown to increase the risk of CVD (18–22) it has been discussed if the MetS is a useful clustering of risk factors (23), and if the syndrome really exists (24). Whether this individual cardiovascular risk factors sum up more than just the additive effect of the single components is controversially discussed.

In the San Antonio Heart Study, including 2815 patients, the risk of death from cardiovascular cause associated with MetS (HR 2.53, 95% CI 1.74;3.67) was similar to the risk associated with impaired fasting glucose alone (HR 2.87, 95% CI 1.96;4.20) (25, 26). On the other hand, Feinberg et al. found higher 30-day mortality rates in acute coronary syndrome (ACS) patients with hyperglycaemia and MetS, opposed to patients with hyperglycaemia without MetS. Upon multivariate analysis, MetS was a strong independent predictor of 30-day (HR 2.54, 95% CI 1.22;5.31) and 1-year (HR 1.96, 95% CI 1.18;3.24) mortality (26, 27). Hence, different combinations of these components might identify very different phenotypes, although the diagnostic criteria of the syndrome are fulfilled (14).

As an example, elevated fasting glucose is a more useful marker for increased risk of diabetes mellitus than any of the other components (14, 28). MetS is a strong predictor of type 2 diabetes (29), with an increased incidence rate of 5 to 7-fold (28, 30). Indeed, the increased cardiovascular risk might develop as a continuum in parallel with increasing fasting glucose, from the normal range via impaired fasting glucose to overt diabetes mellitus (▶Tab. 2) (29).

Importantly, subjects with the syndrome may be classified as having low risk of CVD by both the Framingham score and the European Systematic Coronary Risk Evaluation (SCORE) but still be at increased risk of subclinical atherosclerosis and cardiovascular events (31–33). In a recent meta-analysis including 43 cohorts, the relative risk for cardiovascular events and death was 1.78, with the highest risk in women (relative risk 2.63) (34). After adjustment for traditional risk factors like hypercholesterolaemia and smoking, the syndrome was still associated with increased risk (relative risk 1.54) (34).

With physical inactivity and increased calory intake, especially one of the components of the MetS, obesity, represents a major challenge in the western world today. In the United States abdominal obesity has tripled during the past 40 years (35), more than 25% of the US population can be classified as having the MetS (36) and the prevalence is increasing (37). Depending on which classification that has been used, similar prevalence of the syn-

Tab. 2 American Diabetes Association criteria for the diagnosis of diabetes mellitus

category	plasma glucose in mmol/l (mg/dl)		HbA_{1c} in %
	fasting	2-hour post-load	
normal	<5.6 (101)	<7.8 (141)	<6.5
impaired fasting glucose (IFG)	5.6–6.9 (101–124)		
impaired glucose tolerance (IGT)		7.8–11.0 (141–198)	
diabetes mellitus	≥7.0 (126)	≥11.1 (200)	≥6.5

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drome can be found in India and several countries in Europe, whereas the prevalence is even higher in some Latin-American countries (21 to 43%) and lower in South-East Asia (5). The prevalence is also increasing with age, affecting >40% of US adults above the age of 60 years (11, 38). Accordingly, in several studies the obese have been shown to have a greater cardiovascular risk, compared to their lean peers (5, 37, 39, 40).

Given the rising incidence and the cardiovascular risk associated with MetS, the cellular pathogenesis leading to increased mortality and morbidity is of great interest, especially for the development of novel therapeutic agents.

Atherosclerosis, an inflammatory disease

CVD and its clinical complications, including stroke, myocardial infarction and sudden cardiac death, are the major causes of morbidity and mortality in the Western world today (41). It is now well established that atherosclerosis is an inflammatory disease (41–46). The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries. The earliest type of lesion, the so-called fatty streak, which is common in infants and young children, is an inflammatory lesion, consisting of monocyte-derived macrophages (MDMs) and T lymphocyte s(41). This inflammatory lesion might be triggered through oxidation of low-density lipoprotein (LDL) cholesterol and/or shear stress (41, 42, 44, 45).

The five classic, well established risk factors for the development of CVD, including family history, smoking, hypertension, hypercholesterolaemia and diabetes mellitus, together account for about 50% of a person's atherosclerotic risk (4). The importance of individual variation in inflammatory response for atherosclerotic and cardiovascular risk is becoming an increasingly interesting and exciting new frontier in this area of cardiovascular research.

Cytokines of the interleukin-6 (IL-6) family have been proven to play a pivotal role in inflammation, regulating the formation, progression, and stability of atherosclerotic plaques (47–50). These IL-6 family cytokines – the glycoprotein (GP) 130 ligands – include IL-6, IL-11, oncostatin M (OsM), leukaemia inhibitory factor (LIF), cilary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), IL-27, neurotrophin-1/B-cell stimulating factor (NNT-1), and neuropoetin (NPN), and each cytokine exerts its actions via the homo- or heterodimerisation of the GP130 receptor with a respective cytokine-specific receptor unit (51).

From this extensive number of members of this cytokine family, some of them are of particular interest in atherosclerosis. The pleiotropy of the cytokines involved in this system remains a challenge in the interpretation of their distinct roles in inflammation. Whereas IL-6 has been shown to have detrimental effects in the progression and development of atherosclerosis, LIF and CNTF have been shown to be beneficial, preventing development of experimental atherosclerosis. LIF and CNTF have also been shown to be neuroprotective during experimental stroke (50, 52–57). Also interleukin-18 (IL-18) is a potent pro-inflammatory cytokine which is involved in the modulation of type 1 helper T cell (Th1) response, and a role in plaque destabilisation has been suggested (11, 58, 59). IL-18 is thought to exert its main pro-atherogenic effects by inducing interferon-Y production, which potentiates the inflammatory process and may leads to thinning or inhibition of the fibrous cap formation, resulting in vulnerable, rupture-prone plaques (11, 60, 61). However, data regarding IL-18 as a potential predictor of acute cardiovascular events have so far been conflicting (62, 63).

Moreover, proteases play an essential role in cell migration and tissue remodeling. Recent gene targeting and gene transfer studies in mice have revealed a pleiotropic role of the plasminogen and matrix metalloproteinase (MMP) system in arterial neointima formation, atherosclerosis, aneurysm formation, myocardial ischaemia, angiogenesis, wound healing, tumour growth, metastasis and infection (64, 65). The zymogen plasminogen is the central component of the plasminogen- or fibrinolytic system (66). Two physiological plasminogen activators (PAs) namely tissue-type PA (t-PA) and urokinase-type PA (u-PA) have been identified, which can convert plasminogen to the active enzyme plasmin. Plasmin in turn degrades fibrin and hence dissolves intravascular blood clots (66). However, plasmin can also activate MMPs that subsequently degrade extracellular matrix proteins such as collagens, laminin and fibronectin. In atherosclerosis MMPs, especially matrix metalloproteinase-9 (MMP-9), have been shown to play an important role in destabilising the plaque, which is closely related to thrombotic events (67–69). The most prominent bridge-builders between lifestyle factors, resulting co-morbidities, adipose tissue and atherothrombosis are depicted in (▶ Fig. 1).

Atherosclerosis has previously been regarded as a solely mechanical disorder in which percutaneous coronary intervention and bypass surgery would represent the most promising treatment option. Since inflammation has been identified as the cornerstone for arterial occlusive disease, also therapeutic targets have shifted. As an example, inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) reduce cardiovascular events to a great extent while the physical coronary obstruction remains almost unaffected (70). Moreover, angiotensin-converting enzyme (ACE) inhibitors suppress coronary events out of proportion compared to their blood pressure lowering effects. Angiotensin II is a pro-inflammatory cytokine itself, amplifying the production of reactive oxygen species. In a rabbit model of accelerated atherosclerosis, ACE-inhibitors prevent nuclear factor-kappa B activation and neointimal macrophage infiltration (70, 71).

These examples show how ongoing research paved the way for promising targets in prevention and treatment of atherosclerosis. However, further investigations are needed to identify novel therapeutic agents that reduce the highly specific inflammatory burden of patients prone to CVD.

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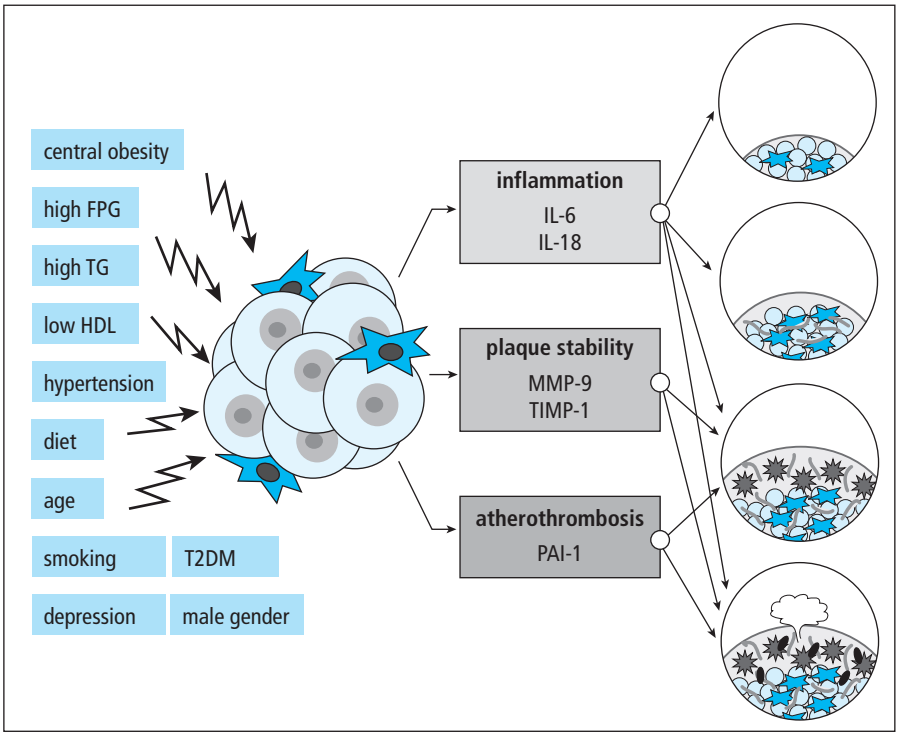

Fig. 1 The bridge-builders between lifestyle factors, co-morbidities and atherothrombosis (FPG: fasting plasma glucose; TG: triglycerides; HDL: high-density lipoprotein; T2DM: type 2 diabetes mellitus; IL-6: interleukin-6; IL-18: interleukin-18; MMP-9: matrix metalloproteinase-9; TIMP-1: tissue inhibitors of matrix metalloproteinases-1; PAI-1: plasminogen activator inhibitor-1)

The role of adipose tissue in atherothrombosis

In the pathogenesis of atherosclerosis, adipose tissue is now recognised as an endocrinologically active organ that produces and releases a variety of pro-inflammatory cytokines, hormones and other metabolic factors (72). The primary physiological inhibitor of plasminogen activation, plasminogen activator inhibitor-1 (PAI-1), has evolved to an early bridge builder between atherosclerosis and adipose tissue (72). Since PAI-1 plays a crucial role in the dissolution of fibrin polymers, elevated levels have been shown to be linked to arterial occlusive disease and atherothrombosis (73).

Accordingly, PAI-1 expression acts as a cardiovascular risk factor (74). Most important, the expression of PAI-1 in adipocytes is mediated through inflammatory cytokines like IL-6 (75, 76). Serum levels of IL-6 are elevated in the obese and strongly correlate with body mass index (BMI) which might point towards low grade systemic inflammation in these subjects (77). Within the atherosclerotic plaque, as well as in adipose tissue, IL-6 and IL-18 are expressed by adipocytes and resident macrophages (43). In order to use them as a marker for atherosclerosis by measuring circulatory levels, both cytokines have been found to independently predict cardiovascular events (43).

Moreover, recent experimental studies indicate an interaction between MMPs and lipid metabolism. MMP-9 has been implicated in adipocyte differentiation and it has been shown to regulate TG release from adipocytes in vitro (78). MMPs have in some studies been shown to cleave apolipoprotein C-II (apoC-II), a cofactor of lipoprotein lipase (LPL), an enzyme involved in TG uptake and metabolisation (79). It has been reported that MMP-9 is correlated with LDL-cholesterol and inversely correlated with HDL cholesterol (80). Furthermore, statins have been shown to influence plasma levels of MMP-9 (81). Given the numerous interactions between MMPs and lipid metabolism, some effects of elevated MMP-9 levels may potentially be exerted through interaction with plasma lipids and adipocyte maturation, in addition to a direct effect on plaque stability (78, 79, 82).

We have recently performed a study aimed to further elucidate the possible connection of selected adipose tissue derived markers, mediators and effectors of inflammation, and presence of CVD (83). In this cross sectional study, a total of 563 men, age 64–76 years, were included and subjected to subcutaneous adipose tissue biopsy for RNA extraction. We compared gene expression values for pro-inflammatory markers – IL-6, IL-18, MMP-9, tissue inhibitors of matrix metalloproteinases-1 (TIMP-1) and PAI-1 – of each individual subject to the median expression level from the entire study population and calculated an "Adipose tissue Pro-Inflammatory Activity" (APPIA) score. The overall inflammatory activity in the adipose tissue assessed by the APPIA score was associated with presence of CVD. Comparing subjects with high inflammatory score to subjects with low or medium inflammation, a statistically significant association with the presence of CVD was found in the multivariate analysis (relative risk 7.9, CI 1.6–38.6; p = 0.01) (83). Moreover, a higher inflammatory score was associated with higher values of intima media thickness (IMT) (83). Analysing the circulating serum protein levels of the same cytokines included in the APPIA score, we did not find any correlation with presence of CVD or IMT.

Although there is data from larger trials, demonstrating circulating levels of inflammatory cytokines to be predictive of CVD (43), one could speculate that adipose tissue derived pro-atherosclerotic and pro-inflammatory markers might mirror gene-expression within the vessel wall more precisely than the conventional analysis of circulatory cytokines. Accordingly, trying to assess the mass of adipose tissue together with its inflammatory activity could provide useful hints towards a pathogenic link between obesity and the presence of CVD.

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Adipokines and atherosclerosis

The discovery of the adipokine leptin in the 1990s set in motion an explosion of scientific interest towards fat as a source of active mediators (84–89). Rather than a simple energy store, it is know recognised that adipose tissue itself acts as an endocrine organ, and the list of known adipokines and their respective functional importance in diseases such as diabetes, MetS and atherosclerosis grows (90). Due to their relationship to adiposity and the increasing worldwide importance of overweight and obesity as medical condition, the relationship and interaction of adipokines with other cytokines, as well as their individual biological functions, is an extremely interesting area of research.

Leptin

Leptin was the first adipokine to be described in 1994 by Zhang et al. It acts predominantly in the hypothalamus, regulating food intake and energy expenditure. Mice lacking of leptin prematurely develop obesity along with hyperphagia, hyperinsulinaemia and hypogonadism (91). In humans, the congenital and treatable deficiency of leptin is very rare and clinical trials have shown that obese patients rather have high levels of leptin combined with leptin resistance, which makes treatment with the recombinant substance unfavourable (92–95). It proportionally correlates with BMI and has been implicated in multiple cardiovascular and metabolic disease processes including myocardial infarction, stroke, hypertension and atherosclerosis, where it is said to act synergistically with other inflammatory mediators (84, 86, 90).

A study in 120 non-diabetic patients by Piatti et al. reported that leptin (and insulin) levels were higher in patients who experiences in-stent re-stenosis, although this effect was not deemed to be statistically significant upon multiple regression analysis (85).

Adiponectin

Low circulating levels of adiponectin (APN) have been linked to coronary artery disease (CAD) (96) and MetS (97), and it is considered to be protective in atherosclerosis, an action probably related to its anti-inflammatory properties (90). Mice lacking of APN are prone to severe neointimal thickening and APN restoration has been shown to diminish that effect (98, 99). Paradoxically, high APN levels were also associated with higher mortality in heart failure patients, a result the authors attributed to its function as a marker of wasting (100). The secretion of APN by adipocytes was inhibited by pro-inflammatory cytokines, and APN down-regulated IL-6, interleukin-8 (IL-8), macrophage inflammatory protein (MIP) 1a/b and macrophage chemoattractant protein (MCP) 1 (90). Moreover, APN may act as plaque stabiliser by up-regulation of TIMP-1 production in macrophages (101).

Several studies have investigated the predictive value of APN in in-stent re-stenosis, with conflicting results. Shimada et al. found that APN levels did not predict re-stenosis after coronary stenting (102), whereas Hong et al. demonstrated that patients receiving sirolimus-eluting stents who were treated with telmisartan had significantly lower levels of APN, as well as a decrease in late lumen loss (103).

Omentin

Omentin was identified more recently, and hence much less is known about its exact function (104–107). Similar to APN, omentin plasma levels and gene expression correlate inversely with obesity, waist circumference and insulin resistance, all markers of the MetS, whilst omentin levels correlate positively with APN and high density lipoproteins (104). In patients with MetS, omentin levels were lower compared to controls and further reduced in patients with MetS and atherosclerosis, as measured by IMT and the presence of carotid plaque (108). The prevention of TNF-α induced cyclooxygenase-2 (COX-2) expression in vascular endothelial cells is one of the anti-inflammatory effects (109).

Resistin

The main action of resistin is to impair insulin sensitivity. Plasma levels of resistin have also been implicated in MetS, unstable angina and as an indicator of poor prognosis in CAD (110–112). The role of resistin in atherosclerosis is said to be related to its induction of pro-inflammatory markers such as endothelin-1, MCP-1 and vascular cell adhesion molecule (V-CAM) 1 (111, 112). Performed in a group of diabetic patients undergoing percutaneous coronary intervention, one study reported that serum resistin levels were higher in the restenosis group (113).

The IL-6 trans-signalling system in the context of metabolic syndrome

As mentioned, the biological function of IL-6 is delivered via a complex interaction of soluble and membrane bound receptors. This is particularly true for IL-6 transsignalling (49). The key players of the IL-6 system are the soluble components IL-6, soluble IL-6 receptor (sIL-6r), soluble glycoprotein 130 (sGP130), the membrane bound IL-6 receptor (IL-6r), and the membrane bound, ubiquitary GP130 (49). IL-6 alone can take effect only in cells that express both, IL-6r and GP130.

Interestingly, only a handful of cell-types, such as macrophages, neutrophils, T-cells and hepatocytes, express IL-6r on the cell surface and therefore interact with IL-6 alone. By contrast to the IL-6r, GP130 is ubiquitously expressed (49). In order to activate signalling cascades downstream of GP130 by trans-signalling on cells lacking of the IL-6r, IL-6 binds to the sIL-6r first, then forming a complex with GP130 (49–51).

It has been suggested that IL-6 mediates its anti-inflammatory activities via traditional signalling, whilst the pro-inflammatory effects, such as recruitment of mononuclear cells are triggered through trans-signalling (49–51). Correspondingly, sGP130 is an independently predicts worsening cardiac pump failure and death, and significant up-regulation of GP130 has been demonstrated in the infarct area in a

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rat myocardial infarction model (114, 115). As recently revealed, hepatic-specific GP130 knockout mice are less prone to atherosclerosis, and this effect is probably related to a reduction in acute phase proteins and macrophage infiltration of the plaques in these mice (47). Although elevated levels of IL-6 have been shown to be associated with the presence of MetS and other established risk factors (7), data about MetS and the different components of the IL-6 trans-signalling system are scarce.

In a recent study on men at high risk of CVD, we found higher circulating levels of sGP130, sIL-6r and IL-6 in subjects with MetS compared to those without. We found a clear association between sGP130 and sIL-6r and increasing components of MetS. Furthermore this association seems to be triggered by different MetS components for each individual cytokine (116). Therefore, the presence of hypertriglyceridaemia, hypertension and elevated FPG was associated with significantly higher levels of sGP130 (116). In order to translate our findings of associations between MetS and increased levels of sGP130 and sIL-6r, we analysed possible correlations to markers of endothelial dysfunction (E-Selectin, intracellular adhesion molecule (I-CAM) 1, V-CAM-1) and arterial stiffness. We found a positive correlation between sGP130, sIL-6r and IL-6, and the mentioned markers of endothelial dysfunction and arterial stiffness, whereas the relationship was independent of the presence of MetS (116).

The individual association between particular cytokines of the IL-6 trans-signalling system, the MetS and its single components sheds light on the complex role of inflammation subjects prone to CVD. The novel link between IL-6, sGP130 and sIL-6r and markers of endothelial dysfunction and arterial stiffness might indicate a role for these cytokines in the early stages of – clinically silent – atherosclerosis.

Interleukin-18 and hyperglycaemia

As mentioned previously, there are several studies showing elevated serum levels of PAI-1, IL-6 and IL-18 in subjects with CVD and MetS (43, 117). The source of IL-6 and PAI-1 partly lies in adipose tissue, whereas the origin of IL-18 is not fully disclosed (117).

A recent study demonstrated that intermittent high glucose has an enhancing effect on IL-18 expression in cultured adipocytes, whereas a previous study suggests non-fat cells to be the main source of IL-18 in adipose tissue (118, 119). Nevertheless, the exact cellular source remains unknown.

IL-18 levels have been shown to rise progressively with the increasing number of MetS components (120) and to predict the development of type 2 diabetes, independent of other pro-inflammatory factors (121). However, conflicting data exist whether IL-18 is a predictor of coronary heart disease and data about patients with MetS are particularly scarce (62, 63).

Trøseid et al. recorded cardiovascular events over three years in an elderly male population with and without MetS. In the total population, CRP, IL-18 and IL-6 were elevated in subjects with events. In subjects with MetS, IL-18 was the strongest predictor (adjusted odds ratio 2.9, 95% CI 1.1;7.8), whereas in subjects without MetS, only CRP seemed independently predictive of cardiovascular events (3.3, 1.5;7.3) (119). Importantly, the predictive value of IL-18 was particularly pronounced in subjects with elevated fasting glucose (119).

We investigated the expression of PAI-1, IL-6 and IL-18 in subcutaneous adipose tissue of subjects with and without MetS. Furthermore, we explored the expression of IL-18 in monocyte-derived macrophages (MDMs) in an in vitro model of hyperglycaemia (122). Expression of IL-18 was increased in subcutaneous adipose tissue of subjects with MetS compared to subjects without. When adjusted for relevant covariates, fasting plasma glucose was the only MetS component being independently associated with the expression of IL-18. In MDMs the expression of IL-18 was increased by 50% when exposed to hyperglycaemia. Our findings indicate that adipose tissue from subjects with MetS have a particular inflammatory pattern, possibly driven by glucose. From our in vitro experiments it might be suggested that MDMs are – at least partially – the cellular source of IL-18 expression amplified by glucose (122).

Since the role of inflammation in atherosclerosis has almost exclusively been studied in visceral adipose tissue (72), this findings indicate an active role of subcutaneous adipose tissue regarding the expression IL-18 in MetS for the first time. The recent finding that IL-18 is predictive of hard clinical endpoints, especially in the presence of hyperglycaemia (119), emphasises the importance of inflammatory processes in adipose tissue.

Matrix metalloproteinase-9 in cardiovascular disease

Over the last decade scientific interest towards MMPs and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs), has rapidly grown, especially since they have been suggested to become therapeutic targets for CVD (123).

MMPs are powerful proteases, capable of degrading most components of the extracellular matrix (124). The integrity of extracellular matrix is crucial for the stability of the atherosclerotic plaque (67, 68). Amongst this vast group of proteinases, MMP-9, a zinc-dependent gelatinase, is highly expressed in atherosclerotic lesions. Mainly derived from macrophages, it has been localised at the shoulder of the atherosclerotic plaque where it might be involved in destabilisation through proteolytic actions (67, 68, 125). The activity of MMPs is tightly regulated by specific TIMPs. In the case of MMP-9 this is mainly effectuated through its specific inhibitor TIMP-1 (67, 68).

Numerous publications point towards a role of MMP-9 in the progression of atherosclerosis and plaque rupture, the most common mechanism of ACS (69). MMP-9 may potentially serve as a diagnostic biomarker for patients presenting with acute chest pain (69), however, larger prospective studies are still required to establish its role in risk stratification of CAD patients. Nevertheless, the association between MMPs and cardiovascular risk factors, such as arterial hypertension, type 2 diabetes, familial hypercholesterolaemia and MetS is evident (33, 126–128).

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We could recently show the importance of MMP-9, TIMP-1 and MMP-9/TIMP-1-ratio on cardiovascular events in elderly men at high risk for CVD (129). After three years of follow-up, elevated levels of MMP-9 (>75th percentile) were stronger predictors of cardiovascular events in individuals with hypertriglyceridaemia (>1.7 mmol/l) (OR 3.69; CI 1.67;8.19; p = 0.001). Significance for trend through quartiles of MMP-9 was only reached in patients with hypertriglyceridaemia, but not in normotriglyceridaemic individuals or the total population (129).

The findings might partly be explained by the ability of several MMPs, including MMP-9, to cleave apoC-II, which results in reduced LPL cofactor activity of apoC-II. LPL physiologically catalyses the hydrolysis of long chain TGs for transport into peripheral tissue. In turn, LPL deficiency causes hypertriglyceridaemia, a well-established risk factor for cardiovascular events (79, 130). Based on the impact of MMP-9 on plaque destabilisation and rupture, MMP-9 inhibition may serve as a novel therapy for atherosclerosis (69). Thus, many recent publications suggest a huge potential of MMP-9 inhibition in cancer treatment, chronic inflammatory disease, and CVD (65, 69, 131, 132).

Platelets, inflammation and atherosclerosis

In the 1960s, the presence of platelets at the site of endothelial injury was already recognised, when retinal embolisms were related to atherosclerosis in the internal carotid artery (133, 134). Although the role of platelets in thromboembolic events is undeniable today, their participation in early inflammatory changes, thus, initiation of the atherosclerotic process, is a young and exciting field of cardiovascular research. We want to shortly address important mechanisms that imply the contribution of platelets to acute and chronic inflammation, subsequently leading to atherothrombosis.

Platelets interact with the endothelium at lesion-prone sites, even when intact, in a well-orchestrated fashion through tethering and rolling, mediated by P-selectin and P-selecting glycoprotein ligand-1 (PSGL-1). After further decrease of velocity by rolling on the activated endothelium, platelets firmly adhere through integrin binding (134–136). Consequently, activated platelets and endothelial cells actively release chemokines, such as monocyte chemoattractant protein-1 (MCP-1), IL-8, CD40 ligand and interleukin-1α (IL-1α), a highly potent inflammatory cytokine (134, 137). In the blood stream, activated platelets recruit leukocytes, leading to leukocyte microparticle formation, an indicator of subclinical atherosclerosis (134, 138). Those leukocyte-derived particles correlated even better with inflammatory markers and MetS than platelet-derived or endothelial-derived microparticles (134, 138). Further, activated platelets secrete stromal-derived factor-1α (SDF-1α), which leads to the recruitment of bone-marrow derived progenitor cells to the surface of arterial thrombi (134, 139). It has been shown that platelet SDF-1á surface expression is increased in patients with ACS, compared to patients with stable angina (134, 140). Depending on circumstances, platelets can not only recruit, but also regulate the differentiation of progenitor cells into endothelial or foam cells at the site of vascular injury (134, 141). Those mentioned and many more pathways indicate the importance of platelets not only in the acute setting of myocardial infarction, but also in the early changes leading to atherosclerosis.

Future directions

A variety of therapeutic approaches are currently investigated in clinical trials. Phase III trials were initiated for darapladib, a lipoprotein associated phospholipase A2 (Lp-PLA2) inhibitor that represents a new class of agents in atherosclerosis. The Lp-PLA2 is abundantly expressed in the necrotic core of plaques, therefore, inhibition of the enzyme might help to lower the risk of cardiovascular event (142, 143). Likewise, dipeptidyl peptidase 4 (DPP-4) has been shown to be present in atherosclerotic plaques and saxagliptin, an approved DPP-4 inhibitor for the treatment of type 2 diabetes, is currently under investigation regarding its effects on supressing inflammatory markers of atherosclerosis (144). Inhibitors of MMPs have been implied in a variety of inflammatory and malignant disease and studies in animal cancer models revealed promising results, that could not be confirmed in phase II-III trials (145). After mostly disappointing results with early broad-spectrum MMP inhibitors, a highly selective MMP-12 inhibitor has been discovered, which considerably delayed the progression of atherosclerosis in mice (146, 147).

Whether compounds alike reach approval to clinical trials for prevention of CVD remains elusive.

Conclusion

Since the seminal work of Ross in 1998, establishing atherosclerosis as a chronic inflammatory disease, the hunt for a marker for early inflammatory changes within the vessel wall has been in focus of biomedical research (41, 42, 44). Consequently, extensive research revealed the pivotal role of the interleukins, MMPs, adipokines and many more inflammatory markers in atherothrombosis. Circulatory, pro-inflammatory proteins, such as IL-6, IL-18, PAI-1, fibrinogen, MMP-9, CD40 ligand, CRP and many more are strongly associated with CVD, endothelial dysfunction and coronary artery disease (43).

Adipose tissue has been shown to actively participate in systemic, low-grade inflammation, as numerous cytokines are released into circulation by resident macrophages, fibroblasts, endothelial cells and adipocytes themselves. The discovery of adipokines in the 1990s set in motion even greater interest towards adipose tissue derived proteins. At present, therapeutic targets for the prevention and treatment of CVD have been concentrated on controlling the well-established cardiovascular risk factors with anti-hypertensives, antidiabetics, statins and antiplatelet drugs. One of the most promising future therapeutic approaches is the inhibition of MMPs, which are claimed to be useful for treating systemic vasculitis, malignant tumors, atherosclerosis, stroke, pulmonary hypertension and heart failure (148).

Nevertheless, the role of inflammation in atherosclerosis is as complicated as the

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disease itself, and the majority of the complex immunological influences and interactions remain to be fully elucidated. The understanding of the complex inflammatory pattern of atherothrombosis may serve as foundation for the development of novel therapeutic agents that target the ultimate source of the disease rather than the precipitating factors.

Conflict of interest

The authors declare that they have no conflict of interest.

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