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Review

REVIEW

Immunotherapy and cardiovascular diseases: novel avenues for immunotherapeutic approaches

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Abstract

As current therapies for cardiovascular disease (CVD), predominantly based on lipid lowering, still face an unacceptable residual risk, novel treatment strategies are being explored. Besides lipids, inflammatory processes play a major role in the pathogenesis of atherosclerosis, the underlying cause of the majority of CVD. The first clinical trials targeting the interleukin-1β-inflammasome axis have shown that targeting this pathway is successful in reducing cardiovascular events but did not decrease overall CVD mortality. Hence, novel and improved immunotherapeutics to treat CVD are being awaited.

Cardiovascular pathologies and immunology: two disciplines born apart?

Immunology and cardiology might seem two different fields of medicine, but they considerably overlay. They stem out of the same fertile soil and only recently researchers started digging into it, clarifying the role of the immune system in cardiovascular pathologies, among which heart failure (HF), myocardial infarction (MI) and atherosclerosis.

Atherosclerosis is defined as a chronic inflammatory disease which determines a slowly progressing formation of luminal plaques in large- and medium-sized arteries. These atherosclerotic plaques may rupture, erode or become unstable leading to fatal adverse events such as ischemic heart disease, stroke and peripheral vascular disease, collectively defined as cardiovascular diseases (CVD). Hence, vascular inflammation participates in atherosclerotic plaque initiation, perpetuation and instability.

Plaque formation is driven by increased blood lipid levels, in particular hypercholesterolemia as well as maladaptive immune responses, determining a state of chronic inflammation in the arterial wall.[1] The disease process occurs predominantly at sites of disturbed laminar flow, i.e. arterial branchpoints and

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bifurcations.[2] The turbulent blood flow can cause endothelial injury and a consequent release of inflammatory mediators. In addition, low-density lipoproteins (LDL) start to accumulate in subendothelial layers and get modified (OxLDL). Through these modifications, LDL gets phagocytosed by macrophages, which transform into the so-called 'foam cells' forming a luminal fatty streak. (Ox)LDL is antigenic and enhances leukocyte recruitment, including T cells and B cells. Lastly, smooth muscle cells migrate to the surface of the plaque forming a fibrous cap.

The use of lipid-lowering drugs such as statins, the hydroxyl-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, and more recently developed proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has shown promising results in the clinic. Both classes of drugs effectively control LDL cholesterol and reduce major adverse cardiovascular events by almost 50%.[3] Nowadays, it has been established that statins also have additional effects. On one hand, they phenotypically determine plaque stabilization by reducing lipid content and a greater fibrous-cap thickness,[4] and this change in plaque phenotype has been associated with an increase in the plaque erosion/plaque rupture ratio;[5] on the other hand, they have potent anti-inflammatory properties. Moreover, clinical studies, such as the *Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin* (JUPITER) corroborate that inhibition of inflammation through statins affects clinical outcomes, independently of lipid lowering.[6]

Furthermore, bempedoic acid, a nonstatin antihyperlipidemic drug developed by Esperion, has been approved in 2020 for the treatment of hypercholesterolemia, as monotherapy or in combination with ezetimibe, an inhibitor of intestinal cholesterol absorption.[7]

However, albeit their effectiveness, a substantial part of the population still suffers from CVD. Hence, during the past decades basic and clinical research have generated a large body of evidence on the possibility of targeting inflammation, the other crucial component contributing to atherosclerosis as a potential therapeutic strategy in the treatment of atherosclerosis. In this review, we highlight the novel avenues for immunotherapeutics in CVD.

Cardiovascular disease and immunotherapy

The journey of immunotherapy in chronic inflammatory diseases commenced by blocking the most prominent inflammatory cytokines involved, being it a cardiovascular, autoimmune or rheumatoid disease. One successful example is the use of targeting tumor necrosis factor (TNF)-α in patients affected by rheumatoid arthritis (RA), a chronic disease that leads to inflammation and progressive joint damage.[8] Treatment with anti-TNF-α antibodies has been considered state of the art for many years, albeit some patients did not fully benefit. Interestingly, targeting inflammation not only attenuated inflammation-associated joint damage but also reduced the risk of CV events in RA patients.[9]

A crucial inflammatory cytokine involved in the pathogenesis is interleukin (IL)-1β, which upregulates downstream inflammatory cytokines, such as TNF-α and IL-6, as well as acute phase reactants, such as C-reactive protein (CRP), fibrinogen and plasminogen activator inhibitor.[10] In 2017, the pivotal *Canakinumab Anti-inflammatory Thrombosis Outcome Study* (CANTOS) trial demonstrated for the first time that targeting the inflammatory IL-1β pathway with the monoclonal antibody canakinumab led to a significant reduction of first recurrent CVD events in patients with prior MI and residual inflammation independent of lipid-lowering therapies.[11] Residual inflammation is clinically defined by a persistently elevated (>2 mg/l) high-sensitive C-reactive protein (hs-CRP). hs-CRP concentrations >1 mg/dl (10 mg/l) indicate clinically significant inflammation, whereas concentrations between 0.3 and 1 mg/dl (3 and 10 mg/l; minor CRP elevation) indicate low-grade inflammation, the typical inflammation which characterizes CVD.

In a prespecified secondary analysis, Ridker *et al.* further provided evidence that IL-1β blockade was capable of reducing CV and all-cause mortality by 31%, but only in patients who achieved on-treatment hs-CRP concentrations below 2 mg/l. In patients with hs-CRP concentrations at 2 mg/l or above, no significant reduction in these endpoints was observed.[12]

Of note, patients enrolled in the CANTOS trial not only have high risk of a first CV event but also remain at higher risk for recurrent eents. The approach of recording just the first CV event underestimated the disease burden of the patient. Therefore, a more recent subgroup analysis of the CANTOS study done by Everett *et al.* aimed at covering this issue. Patients randomized for the CANTOS trial incurred to an endpoint were asked to remain in the trial for its total duration. Initial and subsequent CV events were collected, allowing a broader assessment of the efficacy of canakinumab. This new study demonstrated that hampering inflammation through canakinumab in patients with prior MI and evidence of ongoing subclinical inflammation reduces the total number of serious recurrent CV events, including nonfatal MI and stroke, unstable angina requiring unplanned or planned coronary revascularization and CV death.[13]

Treatment with canakinumab was also effective in lowering levels of IL-6,[14] a central pleiotropic inflammatory cytokine involved in the pathogenesis of multiple inflammatory disorders such as RA and psoriasis.[15] Overall, results obtained through the CANTOS trial demonstrated that targeting inflammation could substantially prevent atherosclerosis-related adverse CV events.[16] However, benefits of treatment have to outweigh the risks. In fact, the attempt of blocking inflammation with canakinumab was accompanied by downsides such as leukopenia, higher incidence of fatal infections or sepsis,[11] which mandates for the development of other, safer anti-inflammatory drugs.

Using an alternative anti-inflammatory approach with low-dose methotrexate (15–20 mg weekly), a disease-modifying anti-rheumatic drugs (DMARDs) previously established to control the clinical activity of RA, did not reduce inflammation in patients with a history of MI or multivessel coronary disease that also had a history of type 2 diabetes or metabolic syndrome. Specifically, among patients with stable atherosclerosis enrolled in the *Cardiovascular Inflammation Reduction Trial* (CIRT), the treatment with low-dose methotrexate did not reduce levels of IL-1β, IL-6 or CRP and consequently did not result in fewer CV events as compared to placebo.[17]

Another drug proposed at blocking the underlying inflammatory diathesis in CVD is colchicine, an inexpensive, orally administered, potent anti-inflammatory drug, known to affect the inflammasome via affecting tubulin organization.[18] While the first *Low Dose Colchicine trial* (LoDoCo)[19] only involved a smaller patient-cohort (532 patients) and was not placebo-controlled, but open-label trial instead, a second study, the *Colchicine Cardiovascular Outcome Trial* (COLCOT) was more elaborate, also in assessing long-term outcomes and safety profile of the drug. In both studies, 0.5 mg/day of colchicine, given on top of other secondary-prevention therapeutic strategies, such as aspirin, clopidogrel and statins, was effective in the prevention of ischemic CV events in patients with stable coronary

disease and a recent MI, respectively. However, the mechanism(s) by which colchicine exerts its anti-inflammatory CV-related effects still remain obscure. Contrary to canakinumab-treatment, colchicine-treatment did not reduce hs-CRP levels or other plasma markers of inflammation as compared to placebo. In line, the treatment effect on the various components of the combined primary endpoint is rather weak and requires further investigations.[20] Nevertheless, results of a further trial named *Low Dose Colchicine trial II* (LoDoCo II) trial demonstrated that low-dose colchicine improves CV outcomes in patients with clinically stable coronary artery disease (CAD).[16] The LoDoCo II trial was, in contrast to the previous mentioned LoDoCo trial an investigator-initiated, randomized, controlled, double-blind, event-driven trial, which however provided confirmation to the LoDoCo trial.[21]

In synopsis, the strategy of anti-inflammatory targeting has been validated, albeit the partly negative results, still elusive mechanisms and the susceptibility to fatal infections mandate for more specific anti-inflammatory strategies.

It is crucial to bear in mind that inflammation also plays an important role in the pathogenesis of other cardiac pathologies such as heart failure (HF) and the consequent cardiac remodeling.[22] HF represents a major cause of hospitalization, morbidity and mortality in developed countries. Similar to the pathogenesis of atherosclerosis, a vicious cycle between inflammation and declining heart function exists. The role of inflammation in HF was firstly recognized by Levine *et al.*[23] in 1990, who reported elevated level of TNF-α in HF patients with reduced ejection fraction (HFrEF) as compared to healthy individuals. Although this inappropriate immune activation and inflammation ought to be a therapeutic target in patients affected by chronic HF, anti-TNF trials with Etanercept, a soluble receptor that binds both TNF-α and TNF-ß, and Infliximab, a monoclonal antibody against TNF-α, yielded disappointing results.[24] Contrarily, more encouraging results were obtained in animal models by targeting the adaptive immunity and hence blocking T cell costimulation with the Cytotoxic T lymphocyte antigen 4 (CTLA4) immunoglobulin abatacept. Through inhibition of T cell costimulation, the pathogenesis of HF was delayed and its severity reduced in aging mice.[25,26]

Inflammation also plays a pivotal role in the pathogenesis of ischemia/reperfusion (I/R) which is a paradoxical exacerbation of cellular damage and death, after the restoration of blood flow to the ischemic tissue. Hypoxia and reperfusion contribute to the expression of several inflammatory cytokines, namely IL-6, TNF-α and IL-1. Animal studies attest the potential beneficial effect of blocking TNF-α for reducing I/R severity. However, a respective clinical trial aimed at blocking TNF-α in human I/R injury has not been reported.[27] Interestingly, toll-like receptor 4 (TLR4), which is a sensor of lipopolysaccharide, has been identified to be an additional enhancer of cardiac injury and inflammation in the setting of I/R injury.[28] In mice, treatment with the specific TLR4 antagonist eritoran reduced M/R injury as well as markers of inflammation,[29] suggesting that TLR4 is an attractive therapeutic target for I/R injury.

In synopsis, immunomodulation after MI seems currently a promising road to unravel. Strategies include blockade of early initiators of inflammation, namely cytokines, chemokines and reactive oxidative species, as well as downstream blockade of the adaptive immune system, including B cells and T cells. Despite the great effort of the scientific community, the plethora of targets, the current timing and the dosage of potential therapies are issues yet to be faced.

The future ahead

Recent clinical trials have proven that inflammation plays an important role in the pathogenesis of human atherosclerosis, and that targeting inflammation for combating CVD has a huge treatment potential (Table 1). Hence, when designing novel effective therapeutic strategies, there is a multitude of options. Here, we will focus on the therapeutic potential of two immunological pathways, that have been proven to be pivotal in atherosclerosis (i) chemokine-induced immune cell recruitment and migration and (ii) immune modulation via costimulatory and coinhibitory immune checkpoints.

Targeting cell recruitment and migration: chemokines

From ancient Greek, diapedesis is the movement of a cell towards an injured or inflamed site and is a crucial process in atherogenesis. When vascular endothelial cells get activated by turbulent blood flow and oxidative stress, leukocytes start to roll, adhere and migrate into subendothelial tissue. This process is carefully orchestrated by a dyad of chemokines and their receptors, which in turn regulate immune responses.[30] As mentioned earlier, during the process of atherosclerotic plaque formation and under hyperlipidemic conditions, LDL becomes oxidized and induces the expression of CXCL1 by endothelial cells. CXCL1 interacts with CXCR2 on myeloid cells, stimulating their recruitment to sites of chronic inflammation. CXCR2 deficient mice and mice with systemic absence of CXCL1 displayed reduced lesion size and macrophage and apoptotic cell content.[31] The same holds true when CXCR2 is specifically knocked down in hematopoietic cells.[32] Effects in mice deficient for the CXCR2 ligand CXCL1 were shown to be similar, with a greater importance of CXCR2 over CXCL1 for macrophage accumulation in established lesions.[33]

The CCL2/CCR2 axis is crucial for mediating the mobilization of classical and inflammatory monocytes.[34,35] Consequently, in mice depletion of CCR2 resulted in less atherosclerotic lesions.[1] Deficiency in both CCL2 and CX3CR1, or CCR2 and CX3CL further reduced plaque burden. Moreover, silencing of CCR2 through siRNA has been shown to be effective in attenuating monocyte mobilization and infarct-related inflammation in mouse models of MI.[36] In fact, chemokines involved in leukocyte migration during inflammation, may also contribute to injury or repair of myocardial tissue after MI. Lack of CCR2, receptor for CCL2 in mice, determines decrease in macrophage infiltration and infarct size compared to wild-type mice.[37] CXCR2 mediates not only neutrophil chemotaxis but also inhibits cardiomyocyte death induced by hypoxia. Thereupon, its role is controversial on myocardial availability during I/R injury, with a slightly predominant damaging effect over tissue protection.[38]

Another strategy showed, that the administration of a non-antagonistic chemotactic protein-1 (MCP-1/CCL2) mutant, PA508 reduces inflammatory monocyte recruitment, thereby limiting neointimal hyperplasia, as well as lower ischemia/reperfusion injury in mice.[39]

In humans, the first clinical trials using chemokine inhibition, have proven the potential for this class of immunotherapeutics for CVD. In a randomized, double-blind, placebo-controlled phase 2a trial (ClinicalTrials.gov Identifier: NCT00715169) using the CCR2 inhibitor MLN1202, a monoclonal antibody which blocks CCR2-CCL2 interactions, reduced CRP levels in patients with atherosclerotic CVD, defined as

Table 1. Approved anti-inflammatory therapies for cardiovascular disease

Therapeutic agent	Mechanism of action	Effects	Study/clinical trial
Canakinumab	IL-1β antibody	Reduction of inflammation and recurrence of CV events	CANTOS (Ridker et al.)[11]
Methothrexate (DMARD)	Inhibitor of purine metabolism	No beneficial effects	CIRT (Ridker et al.)[17]
Colchicine	Tubulin disruption	Prevention of ischemic CV in patients with stable CAD, no reduction of hs-CRP	LoDoCo (Nidorf et al.)[19] LoDoCo II (Nidorf et al.)[21] COLCOT (Tardif et al.)[20]

>2 risk factor for atherosclerotic CVD and circulating CRP levels >3 mg/l).[40]

CCL5 and CXCL4 chemokine signaling mediates integrin activation and leukocyte arrest on inflamed endothelium. Activated platelets deposit CCL5 on the endothelial surface, with consequent leukocyte recruitment.[35] The interaction of CCL5 with its receptor CCR1 and CCR5 requires sialylation hereby creating favorable and improved ligand-receptor interactions. Mice with a deficiency in sialyl-transferase St3Gal-IV display lower monocyte adhesion and atherosclerotic lesion size in a CCL5-related fashion.[41] The same outcome is also visible when globally blocking CCR5 in mice using Met-CCL5[42] or in mice with CCR5 deficiency.[43]

Accordingly, a Phase 4 clinical trial (ClinicalTrials.gov Identifier: NCT03402815) demonstrated an effective antagonism of CCR5 with the FDA-approved drug maraviroc previously used in HIV infected patients. The administration of the drug (300 mg per os for 24 weeks) combined with antiretroviral therapy (ART) suggested an antiatherosclerotic effect, reflected by improvement of baseline carotid lesions of patients enrolled in the study.[44] Those patients were infected with HIV and treated with ART, which both contributed to an increase in atherosclerosis and activation of chronic inflammatory processes[45,46] and coinfected with hepatitis C virus (HCV), which may also contribute to increased CVD risk.[47]

Another pivotal chemokine dyad involved in cell trafficking and immunity is CXCR4-CXCL12, which has a protective role in cells of the arterial wall by sustaining endothelial integrity and promoting contractile properties of vascular smooth muscle cells. In humans, regression analysis identified the C-allele of SNP rs2322864 in the *CXCR4* locus to be associated with reduced CXCR4 expression in carotid artery plaques and a higher risk of coronary heart disease. Moreover, reduced expression of CXCR4 in carotid plaques correlated with a higher prevalence of symptomatic disease,[48] suggesting that selective modulators of arterial CXCR4 might be a novel therapeutic option to treat atherosclerosis.

In line, a more recent study conducted by Kontos *et al.* proved the efficacy of a soluble engineered molecule (msR4ML1) able to selectively block the interaction between macrophage migration inhibitor factor-1 (MIF-1), an atypical chemokine promoting atherosclerosis through CXCR4. This novel strategy showed promising results in hampering the MIF-1/CXCR4 interaction, without disrupting the atheroprotective effect of the CXCR4-CXCL12 axis.[49]

In conclusion, due to their crucial role in mediating cell trafficking and inflammation, targeting chemokine-chemokine receptor interactions is a promising option to treat atherosclerotic CVD (Table 2A). Albeit the redundancy of the chemokine system, it is of paramount importance to correctly select the target and the drug dosing, which both constitute the main barriers for developing efficacious chemokine-based anti-inflammatory therapies.[53]

Targeting adaptive immunity: immune checkpoints

Immunotherapy targeting the adaptive immune system has recently revolutionized the world of cancer therapy, considerably improving patients' survival, with many drugs targeting immune checkpoints in preclinical and clinical trials, aimed at improving immune responses against cancer cells to promote their killing.[54] These results reflect the strong therapeutic potential of this class of immune modulators. Although targeting immune checkpoints has been rapidly integrated in oncology treatment, its exploitation in CVD is still in a preclinical stage.[55] The two largest classes of immune checkpoints are costimulatory and coinhibitory molecules, and are both master regulators of immune responses, classically known as 'signal 2' that promotes or dampens T-cell activation and proliferation upon T-cell antigen presenting cell interactions,[56] but nowadays known to play a pivotal role in the communication and activation of a plethora of cell types, including immune and nonimmune cells.[57]

Many costimulatory and coinhibitory molecules, including the CD80/86-CD28/cytotoxic T lymphocyte-associated antigen 4 (CTLA4), CD40-CD40L, CD27-CD70, OX40L-OX40, GITR-GITRL and PD1-PDL1/2 axis have been shown to mediate atherogenesis in a laboratory setting[57] (Table 2B). Only recently, the first clinical studies, conducted in other diseases, have revealed the potential of targeting these immune checkpoints in human CVD.

Abatacept, an IgG1-CTLA4 fusion protein that blocks CD80/86 mediated costimulation is an FDA approved drug indicated for the treatment of autoimmune diseases and particularly effective in RA patients that respond poorly to methotrexate or anti-TNF-α treatment.[58]

Data obtained from RA trials show a beneficial effect of abatacept on CVD outcomes. In a study comparing biologics with synthetic DMARDs, abatacept treatment resulted in a significant reduction of CVD (HR 0.5, 95% CI 0.30–0.83).[59] Also, abatacept reduced CVD risk in anti-TNF-α nonresponders in a 2-year follow-up in MI, MACE, stroke and HF compared to rituximab users.[9] Similar results were found in a study where RA patients using TNF-α inhibitors were compared to abatacept users and abatacept was associated with a 20% reduced risk of MACE.[60] However, clinical trials testing the effect abatacept on CVD outcomes directly are still being awaited.

Antibodies that antagonize the coinhibitory CTLA4 and/or programmed cell death protein 1 (Ligand) (PD1(L)), the so-called immune checkpoint inhibitors, are a first-in-line treatment for an increasing number of malignancies. Immune checkpoint inhibitors release the brake on T cell activation, elicit strong

Table 2. Potential anti-inflammatory therapeutic targets: (A) chemokines, (B) immune checkpoint modulators

A		Mechanism of action	Effects
Chemokines	CCR2	siRNA (Majmudar et al.)[36]	Attenuates monocyte mobilization and infarct-related inflammation in mouse with MI
		CCR2 inhibitor, MLN1202 (Clinical trial NCT00715169) (Gilbert et al.)[40]	Reduced CRP in patients with atherosclerotic CVD
	MCP1/CCL2 mutant	Nonantagonistic chemotactic protein PA508 (Liehn et al.)[39]	Reduction of neointimal hyperplasia
	CCR5	CCR5 antagonist Maraviroc (Clinical trial NCT03402815) (Maggi et al.)[44]	Improvement baseline carotid lesions
	MIF-1	soluble engineered molecule (msR4M-L1) by Kontos et al.[49]	Hampering CXCR4/MIF-1 interaction resulting in atheroprotection
B			
Immune checkpoints	CTLA4	Abatacept (CTLA4-IgG1) (Hsieh et al.)[9]	Significant CVD reduction in anti-TNF-α nonresponders
	CD40-CD40L	CD40L antibody (Lutgens et al.)[50]; Schönbeck et al.)[51]	Transformation of unstable plaque into more stable, lipid poor and collagen rich plaques
	CD40-TRAF6	Small molecule inhibitor (Lutgens et al.)[52]	Stable atherosclerotic plaque phenotype

antitumor immune responses, but also cause immune-related adverse events.[61,62] Cardiovascular complications are not uncommon after ICI therapy[63,64] and a recent study among 2842 patients who received ICI treatment or not reported that the incidence of atherosclerotic CV events, defined as a composite of MI, coronary revascularization and ischemic stroke, was increased 4.7-fold after ICI therapy.[65] These studies not only show the potent role of CTLA4 and PD(L)1 as protectors of CVD but also increase awareness of the detrimental side effects of this highly potent anticancer immunotherapy.

Another costimulatory immune checkpoint that can be considered a potent therapeutic target in CVD is the CD40L-CD40 dyad. In an experimental setting, inhibition of CD40L or CD40, even when inhibited in established atherosclerosis, is highly effective in reducing atherosclerosis, and generates plaques that are rich in collagen and contain a limited number of immune cells, the murine equivalent of a stable, clinically safe, plaque.[50–52,66] Although blocking CD40L or CD40 in human CVD seems evident as a potent immunotherapy for CVD, this has never been evaluated in clinical trials. However, antagonistic CD40L and CD40 antibodies, such as CDP7657, VIB4920 and iscalimab are available and have been successfully tested in a plethora of other chronic inflammatory diseases, such as multiple sclerosis, Sjogren syndrome, SLE and transplant rejection, and the outcomes of phase II and III trials are being awaited and therefore, effects on CVD outcomes in these study populations are not yet available. However, preclinical studies, with CD40L and CD40 antagonists designed to target atherosclerotic CVD, have been performed. CD40 does not have intrinsic signal capabilities and needs adaptor molecules, the TNF-receptor associated factors (TRAFs), to exert signaling. Using mice specifically lacking CD40-TRAF6 or CD40-TRAF2/3 interactions, it was shown that only mice deficient in CD40-TRAF6 were protected against atherosclerosis,[52] show that especially CD40-TRAF6 interactions, that predominantly take place in macrophages, drive atherosclerosis. A small-molecule inhibitor (SMI) that targets CD40-TRAF6 signaling[52,67] was designed, and was shown to reduce (existing) atherosclerosis in mice, and induces a stable atherosclerotic plaque phenotype, without causing immune-suppressive or thrombo-embolic side effects.[68] This SMI's specific delivery to macrophages using HDL nanobiologics stabilized atherosclerotic plaques in mice and was proven safe in nonhuman primates[69] and is currently being developed for in-human treatment. A plethora of preclinical data shows that antagonizing the CD40L-CD40 pathway has a true potential as an immunotherapeutic target to treat CVD. Phases I–III trials have revealed that targeting CD40L or CD40 in humans is safe and well-tolerized.

Synopsis

The increasing interest in the field of cardio-immunology is fueled by the growing awareness of the role of inflammation in cardiovascular pathologies, especially atherosclerosis. Although the CANTOS trial has provided evidence of lowered MI-, stroke- and cardiovascular risk, treatment with canakinumab did not reduce overall CV mortality. Given the adverse events after treatment with canakinumab, immune functions deleterious in the cardiovascular system may be necessary for host defense. Hence, novel immunotherapeutic targets need to be developed and tested for their potential and safety in CVD. Based on a large amount of preclinical and scattered clinical data, targeting chemokines or immune checkpoints might result in a better and more safe reduction of atherosclerosis-associated CVD.

Although the time is right to introduce immunotherapy as a valid treatment option for CVD, one always needs to bear in mind that immunotherapy itself in CVD is a double-edged sword, and that therapeutics should be tailored in terms of targets and drug delivery.

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