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Inflammatory response post-myocardial infarction and reperfusion: a new therapeutic target?

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Inflammation is a cornerstone of the post-myocardial infarction healing process. However, an exuberant systemic as well as loco-regional inflammatory response may have a direct deleterious effect on myocytes extending myocardial necrosis and thus altering long-term prognosis. For many years, this overwhelming inflammatory reaction has been proposed as pharmacological target. In animal models, encouraging results have been obtained. However, in human trials, none of the applied medications reached a convincing clinical impact.

Nevertheless, this therapeutic strategy remains conceptually valid, especially in the era of reperfusion by percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI). In this ischaemic setting, the inflammatory response in the peri-necrotic zone may extend the myocardial scar formation, thus playing an important prognostic role.

Not surprisingly, the combination of available and new anti-inflammatory treatments, systemically administrated or locally applied, in association with primary PCI as reperfusion therapy is currently under intensive evaluation. Some promising preliminary results suggest that this treatment modality is likely to become standard care of AMI in the near future.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the western world with more than 1.4 million of new diagnosed cases per year.[1] Acute myocardial infarction (AMI) and unstable angina have progressively become a major concern because of their high prevalence and mortality as well as their high related costs.[1]

Atherosclerosis is mostly the underlying pathogenesis of CAD leading to acute coronary syndrome (ACS). For many years, atherosclerosis has been recognized as a dynamic inflammatory disease involving all vascular beds.[2]

Further correlation of this inflammatory response with acute coronary events could be established as well as a direct correlation with early and late post-ACS major adverse cardiac events (MACE). This suggests that inflammation is also a poor outcome marker in the post-MI setting.[3]

The inflammatory process is not only implicated in the plaque formation, but also plays an important role in the myocardial healing process after an acute ischaemic event.[4]

Inflammation participates in the physiological myocardial scar formation. However, in the case of an exuberant inflammatory reaction, the extent of the primary ischaemically damaged myocardial tissue may paradoxically increase.

Coronary angiography and percutaneous coronary intervention (PCI) have become the best modalities for the detection and the treatment of both CAD and AMI.

PCI provokes plaque fissuring leading to a vessel wall infiltration of lymphocytes and macrophages, both responsible for the post-PCI local vascular inflammatory response.[5]

Myocardial ischaemia due to coronary lumen narrowing or abrupt closure in case of AMI, leads to a systemic

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humoral as well as a more loco-regional cellular inflammatory response, aiming to promote the local myocardial healing process. Both systemic and loco-regional responses are triggers of a complex myocardial inflammatory reaction.

This delicate equilibrium of the loco-regional myocardial inflammatory response, in conjunction with the post-MI systemic inflammatory reaction, is one of the most important steps for a balanced post-MI healing process and finally for a better patient outcome.

This article will try to review the post-MI inflammation pathophysiology, giving also an update of the nowadays-available compounds to control this post-MI inflammatory response.

Regional inflammatory reaction

Post-ischaemic myocardial response

The complex loco-regional myocardial healing process can be schematically divided into four distinct phases.[6,7]

(i) Necrotic phase: acute cell death secondary to necrosis and apoptosis (immediately after MI).
(ii) Acute inflammatory phase: inflammatory response in order to absorb necrotic tissue (1–7 days).
(iii) Sub-acute granulation phase: granulation tissue formation consisting of proliferating myofibroblasts, which increase the myocardial tensile strength and promote blood vessel proliferation thereby improving tissue perfusion and cell survival (1–3 weeks).
(iv) Chronic scar phase: fibroblasts formation and micro-vessel regression generating the final collagen-rich scar tissue (>1 month).

Myocardial necrosis leads also to a systemic activation of the humoral system increasing the regional inflammatory response during an ischaemic event.[4]

Three types of myocardial damages are observed according to the duration, extension, and location of the ischaemia.

(i) Myocytolysis: in the case of a chronic prolonged ischaemia, several myocardial ultra-structural changes modifying the myocyte's contraction capacity are observed. These alterations are directly related to a shortening of the action potential, to an intracellular acidosis, and to a diminished free calcium level. If ischaemia persists, these changes induce an irreversible injury, leading to cellular vacuolization and finally to cellular lysis.
(ii) Coagulation necrosis: observed in the central zone of an ischaemic area.
(iii) Contraction band necrosis: observed in the peripheral myocardial areas following a re-established coronary and a micro-vessel flow (i.e. reperfusion).

Despite the undisputable utility of reperfusion limiting the expansion of an ischaemic area, reperfusion may promote a number of cardiac adverse events limiting its beneficial action. In fact, reperfusion may accelerate the cellular death of some myocardial cells.

These myocardial reperfusion injuries are mainly due to an increase of oxygen-free radicals and to an increase of intracellular calcium, both leading to a significant alteration of the cellular metabolism. Therefore, in ischaemic myocardium, we deal with a so-called 'oxygen paradox', where oxygen is mandatory for cellular survival but it may also be responsible for a direct myocardial injury.

Reperfusion also participates in the development of the 'no reflow' syndrome sometimes observed in the post-PCI setting, and it may further provoke some deleterious myocardial micro-haemorrhages, especially within the necrotic zone.

Although some treatments have shown some promise in the myocardial/reperfusion injury animal model, in human, the complexity of these responses has become a major challenge for novel therapeutic developments targeting different steps of the inflammatory response.

Systemic inflammatory reaction

The systemic inflammatory reaction is composed of a humoral as well as of a cell-mediated response.

Humoral inflammatory response

Cytokine

Cytokines are polypeptides produced by ischaemic myocardium, liver, activated macrophages, and lymphocytes as well as adipose tissue (*Figure 1*).[8]

Important cytokines like tumour necrosis factor-alpha (TNF-α), interleukine-1 (IL-1), and IL-6 are the starting promoters of the humoral post-MI healing process. They directly interfere with the myocardial contractility, the vascular endothelial function, and the recruitment of other inflammatory cells.

TNF-α production in the acute post-MI phase is mainly triggered by ischaemia and several other factors (e.g. mechanical stress deformation of damaged myocytes, reactive oxygen species, auto-regulating self amplification).

In normal condition, the heart does not express cytokines; however, during an ischaemic event, they may be up to 50 times in the culprit ischaemic region and up to 15 times in the adjacent 'non-ischaemic' zones.

In the early post-MI phase, a certain degree of cytokines production is physiological, because in this phase, cytokines play an important cyto-protective role by reducing cell apoptosis.[9–11]

Usually, in the case of small MI, tissular cytokine levels rapidly return to zero. In larger MI, cytokines may persist at very high levels and further being long-time detectable also in the normal adjacent myocardium. This phenomenon produces an unfavourable myocardial remodelling finally worsening clinical outcomes.

Cytokines also play pivotal roles in the pathogenesis of atherosclerosis. However, some may exhibit an

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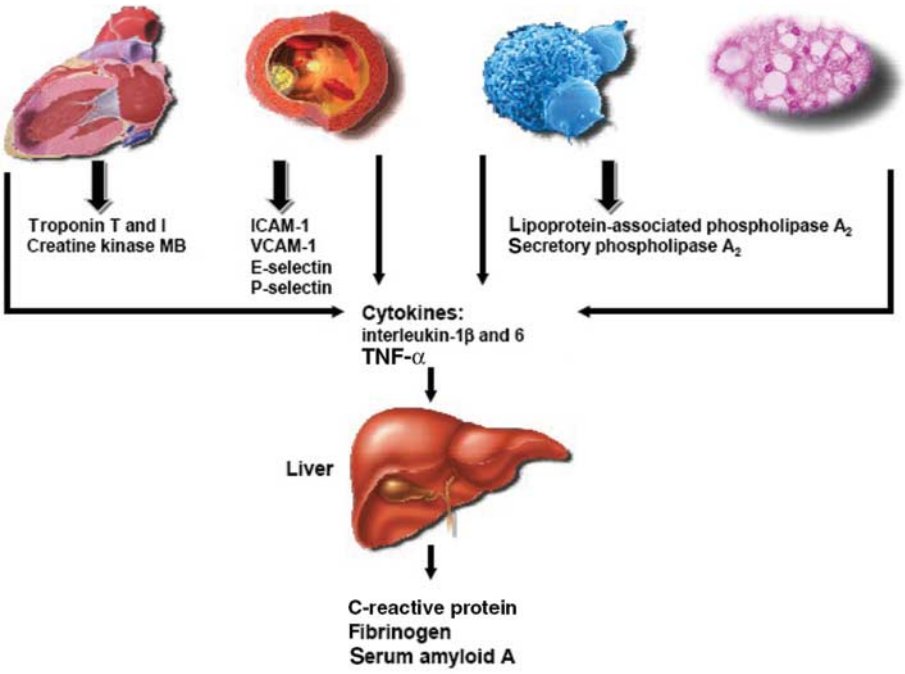

Figure 1 Sources of inflammatory markers and cytokines. Inflammatory markers (C-reactive protein, fibrinogen, serum amyloid A) originate in the liver and their production is stimulated by systemic cytokines (IL-1β, IL-6). These cytokines, as well as others, are produced in several extra-hepatic sites (heart, vessel wall, macrophages, adipose tissue). In response to injury, the heart secretes troponins and creatine kinase MB. The atherosclerotic vessel wall produces soluble adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1 (VCAM-1), E-selectin and P-selectin, and macrophages phospholipases. Modified from *N Eng J Med* 2000; **343**:1179.[84]

anti-atherogenic and anti-inflammatory effect by directly inhibiting TNF-α and IL-6 production (e.g. IL-4, IL-10).[4]

Complement system

The complement cascade represents an essential part of our immunity system. This complex protein system (>30 proteins involved, 5% of all plasma proteins) may trigger various strategic biological activities essential for a correct immunological response (e.g. trigger of the inflammatory reaction, elimination of apoptotic cells and other molecules, phagocytosis and destruction of pathogenic microorganisms and virus).

Proteins involved in the complement system are produced from many types of cells [e.g. hepatocytes (95% of the production), macrophages, fibroblasts, and adipocytes] suggesting that complement not only acts quickly and locally but also plays an important role in the overall systemic immunological defence.

Plasma circulating complement factors are generally in a non-activated form, and their activation represents one of the first defence reactions of the immunological system.

Activation of the complement system occurs via the classic or the alternative pathway (*Figure 2*).

The systemic inflammatory response via the complement components may also stimulate the vascular permeability, the leucocytes chemotaxis, some phagocytotic processes, and the membrane attack complex (MAC).

The complement cascade activates the production of cytokines (e.g. IL-8) which, together with platelet-activated factor produced by the endothelial cells, stimulates endovascular adhesion of neutrophils, thus increasing vascular and tissular inflammation.[12,13]

The complement cascade plays, therefore, a leading role in the physiological systemic and loco-regional inflammatory response.

However, an exuberant regional inflammatory response may have some deleterious effect on the affected zone. In fact, as observed during heart attack, the necrotic myocardial size increases in presence of an overwhelming complement activity, suggesting that complement is also one of the main mediators of the post-MI/reperfusion myocardial injury.

In the case of coronary reperfusion, the local myocardial inflammatory degree may be paradoxically increased, thus clinical outcomes paradoxically worsened.[14,15]

Cell-mediated inflammatory response

Myocardial inflammation is histologically characterized by tissular accumulation of circulating leucocytes, which, once stimulated by the vascular endothelium, migrate through the vessel wall into the ischaemic myocardial region.

The adhesion of leukocytes to the damaged vascular endothelium results in a massive migration of these inflammatory cells (e.g. neutrophils, monocytes, mast cells) into the ischaemic myocardium, thus increasing myocardial tissular inflammation. This endothelial adhesion and trans-vascular migration process may be favoured by spontaneous or PCI-induced coronary plaque rupture.[16]

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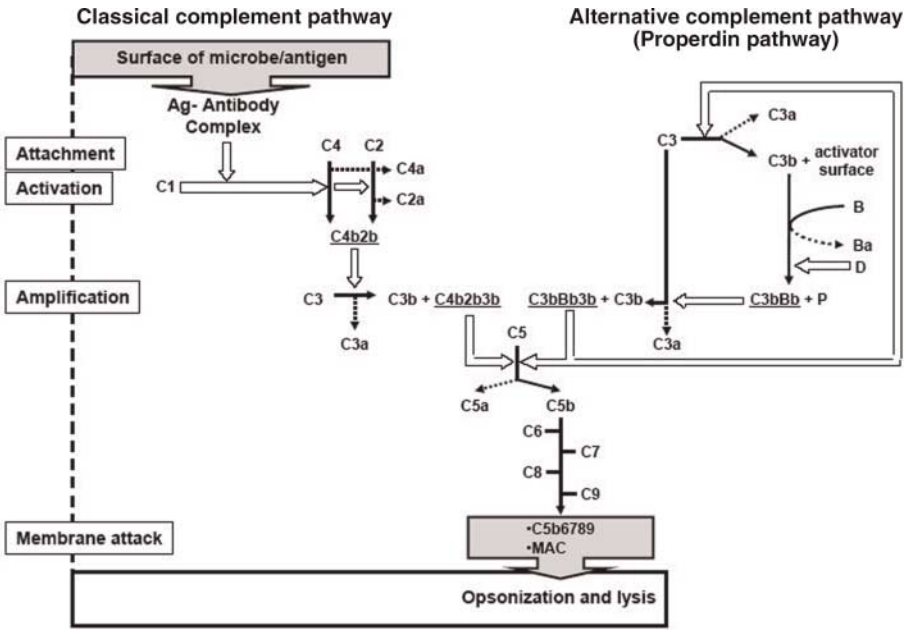

Figure 2 Classic and alternative pathway of the complement cascade. *Classic:* the classic pathway is initiated by the binding of C1 to the antigen–antibody complex, followed by an activation and amplification: C1 cleaves C4 and then C2 to form C3 convertase (C4b2a). The C3 convertase serves to amplify the system: C3 molecules are cleaved to become opsonins (C3b) or to form the C5 convertase (C4b2b3b). The cleavage of C5 leads to the formation of the MAC. The generated opsonins (C4b and C3b) promote phagocytosis of the pathogen. The anaphylatoxins C3a and C5a promote the inflammatory response. *Alternative:* after C3b is generated, it can bind factor B. Factor D can then cleave factor B to form the C3 converatse (C3bBb). The attachment of properdin (P) stabilizes the complex and allows it to generate more C3b. C3 converatse can be additional C3b to produce C5 convertase (C4b2a3b). Modified from The complement system. *Immunology Scope Monograph*. Kalamazoo; 1992.[85]

Neutrophils

Neutrophils' infiltration into the myocardial ischaemic regions may increase the infarction size by promoting tissular inflammation and by their direct entrapment in the capillary micro-vessels, both leading to a reduced myocardial local perfusion.[16,17] Furthermore, local neutrophils' accumulation may also increase thromboxan B2 (TxB2) or other toxic substances production, which may lead to local vasoconstriction and platelet aggregation.[4]

These phenomena are frequently present after PCI and may be co-responsible for the 'no reflow' syndrome observed in the AMI setting.

Monocytes/macrophages

After migration of monocytes into the myocardial tissue, they become active macrophages, which may release a variety of inflammatory substances, cytokines, and growth factors.[8,18] Intravascular circulating monocytes as well as macrophages contained in atheromatous plaques actively participate in the post-ACS or post-PCI inflammatory healing process.[19]

Mast cells

Mast cells are stimulated by the complement 5a (C5a)-adenosine-reactive oxygen complex, which is a necessary element for the development of the myocardial stunning process often observed in a post-ischaemic setting.

Mast cells are therefore actively implicated also in the post-MI inflammatory response. In fact, by degradation, they may release vascular endothelium growing factors, fibroblast growing factors, and histamine, all promoting elements of myocardial fibrosis and angio-neogenesis. During this fibrotic angio-genetic process, myofibroblasts contribute to the extra-cellular matrix and the neo-vessel formation aiming to constitute the final myocardial scar tissue.[4,20]

Inflammatory markers

Systemically circulating cytokines (e.g. TNF-α, IL-6), originating from different organs (e.g. heart, vessel wall, macrophages), stimulate the liver to produce several inflammatory markers (e.g. C-reactive protein, serum amyloid A) which can be easily measured in blood and used to quantify the systemic inflammatory reaction (*Figure 1*).

C-reactive protein: in the case of an AMI, serum C-reactive protein increases following cytokines activation and binds to the damaged myocardial cells. Further, it stimulates the complement cascade, which may finally increase the MI size, worsening the overall post-MI outcomes.[2,21,22] These events suggest that C-reactive protein is not only a sensible inflammatory marker, but should also be considered as a direct inflammatory promoter[23] with pro-atherogenic[24] and pro-thrombotic properties.[25] In fact, C-reactive protein has been shown to be directly correlated to the early and late post-MI morbidity and mortality.[5,26]

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Interleukine-6: interferon gamma (IF-γ), IL-1, and TNF-α stimulate the production of IL-6, which triggers the inflammatory response and the platelet aggregation.[2,27] This inflammatory cytokine, produced from the monocyte/macrophage complex, stimulates the proliferation of the vascular smooth muscle cells (SMC) which have also some pro-coagulant effect.[28] Through hepatic metabolism, IL-6 becomes C-reactive protein, which is easily measured in standard laboratories as inflammatory marker and therefore commonly utilized in daily practice.

Specific anti-inflammatory treatments

Many anti-inflammatory drugs have been already tested in experimental settings and clinical trials aiming to diminish the post-ischaemic loco-regional and systemic myocardial inflammatory response and thus improving outcomes. Despite very encouraging results in animal models, human trials have failed so far to prove consistent benefits concerning cardiovascular morbidity and mortality. However, new molecules are under evaluation with very promising results.

The migration of circulating inflammatory cells through the vessel wall into ischaemic myocardium is a promising new therapeutic target for improving post-MI outcomes; therefore, many of the anti-inflammatory drugs, in addition to their own classic anti-inflammatory properties (e.g. prostanoid production inhibition), may also actively alter this endothelial cell adhesiveness, diminishing the tissular cellular migration and therefore potentially reducing local inflammatory response.

Non steroidal anti-inflammatory drugs and steroids

The site of action of the different anti-inflammatory compounds is summarized in *Figure 3*.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) diminish the leukocyte adhesion on the vascular endothelium and inhibit cyclo-oxygenase (COX) receptors impairing the transformation of arachidonic acid into prostacyclin, prostaglandins, and thromboxanes (necessary for platelet adhesion).[2]

COX-1 receptors are ubiquitarious, contrary to COX-2 ones which prevail in inflammatory sites (e.g. atheromatous plaques).

The first reported trial utilizing NSAIDs in AMI setting was performed in 1981,[29] followed by several other trials aiming to diminish the systemic inflammation and hoping to improve clinical outcomes.

The classic NSAIDs (e.g. diclofenac, ibuprofen) inhibit equally COX-1 and 2 receptors, with a probable cardiovascular neutral effect.[30,31]

Even if still controversial, NSAIDs do not seem to diminish the risk of MI in humans. Interestingly, however, the sudden stop of these drugs, following a chronic administration, may increase this risk.[30–32]

Aspirin. Aspirin has anti-platelet and anti-inflammatory properties by reducing the IL-6 and C-reactive protein levels and by binding to COX 1 and 2 receptors. Aspirin, with its known beneficial cardiovascular effects, inhibits especially the COX-1 receptors efficaciously diminishing the MI risk, especially in an active inflammatory setting (i.e. if high C-reactive protein level: MI relative risk reduction (RRR) of 60%, if normal C-reactive protein level: RRR of 16%).[5]

Selective COX-2 inhibitors

The new selective COX-2 inhibitors do affect less the COX-1 pathway; therefore, they selectively block the prostacyclin production and affect less the thromboxane A_2 synthesis. Therefore, this may favour a prothrombotic state and systemic vasoconstriction.

These pathophysiological mechanisms seem both correlated with an increased CV risk, as observed in several randomized trials, where COX-2 selective inhibition with rofecoxib, celecoxib, or valdecoxib has shown to significantly increase the follow-up associated MACE. Interestingly, this increased CV risk was observed in the first 90 days of treatment.[33–36]

Steroids

Steroids have potent anti-inflammatory properties. They affect the circulating platelets, SMC proliferation, and collagen synthesis.[37]

Prednisone diminish the MI size in the dog model;[38] however, this benefic effect was not observed in human trials, in which an astonishing increased MI size and mortality was observed.[39]

Other cardiovascular drugs

Statins

Statins are nowadays well recognized for their anti-inflammatory properties, the so-called pleiotropic effect. This pleiotropic effect is mainly due to a diminished C-reactive protein level (not IL-6 level),[40] vessel vasomotricity, expression of COX-2 receptors, degradation of collagen, as well as due to an increased NO production, which plays an important role in the myocardial/reperfusion injury model.[2,5,41]

Statins were also shown to diminish the harmful effect of IF-γ and TNF-α[42] and to reduce the PCI peri-procedural micro-infarction, especially in the presence of high C-reactive protein levels.[43] Interestingly, at 1 month after stopping a chronic statin therapy, the MACE rate may be significantly increased in patients with high cardiovascular risk.[44]

ACE-inhibitor and angiotensin II receptor antagonists

In humans, inhibition of the renin–angiotensin system (RAS) improves endothelial function and diminishes the oxygen-free radical production caused by angiotensin II, thus improving plaque stability.[2] RAS inhibition diminishes cytokines' levels.[45] Therefore, ACE-inhibitors and angiotensin II receptor antagonists seem also to have an anti-inflammatory effect, improving the target vessel revascularization rate in the post-PCI setting[46]

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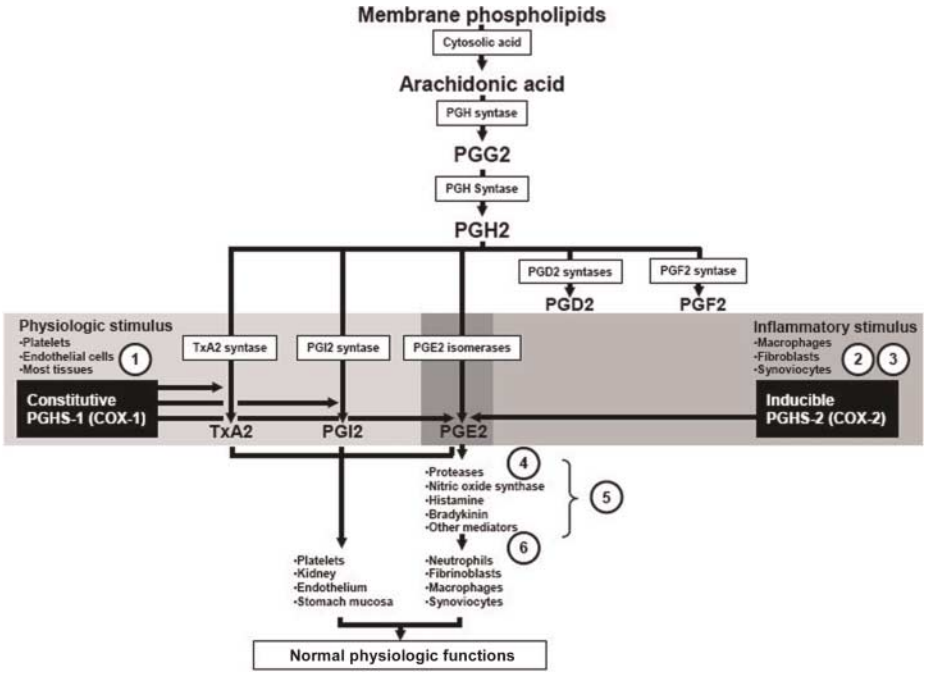

Figure 3 Prostanoid synthesis and inhibition. Representation of the prostaglandin synthetic pathways and the enzymes that catalyze their specific reactions. The site of action of the different anti-inflammatory compounds in the prostaglandin metabolism is depicted. 1, aspirin and other non-steroidal anti-inflammatory drug (NSAID); 2, alternative fatty acid substrate; 3, glucocorticoids and selective COX-2 inhibitors; 4, prostanoid receptor antagonists; 5, nitric oxide synthase inhibitors, antihistamines; 6, monoclonal antibodies to adhesion molecules. PG, prostaglandin.

and reducing the myocardial reperfusion injury in the post-MI setting.[47]

Antioxidant agents

Antioxidant agents like beta-carotene and vitamins E and C may diminish the LDL particles oxidation, consequentially diminishing systemic inflammation. Diets rich in antioxidants elements, such as the Mediterranean diet, due to its high concentration of omega-3 class of essential fatty acids, may reduce MACE in the follow-up. However, these molecules so far did not show enough clinical benefit neither in progression–regression trials nor in clinical event oriented trials.[2,48]

Anticoagulant and anti-platelet regimens

Low molecular weight heparin and unfractioned heparin

Low molecular weight heparin (LMWH) and unfractioned heparin (UFH) act mainly by reducing intravascular haemostasis, but these drugs have also some interesting tissular anti-inflammatory effects with proved clinical benefit in ACS patients.[5,49]

LMWH, more than UFH, favours NO production and inhibits the complement cascade activation, thus diminishing inflammation. Mainly for these anti-inflammatory peculiarities and not for their proper anticoagulants effects, LMWHs may be more efficacious in ACS (i.e. during an inflammatory setting) than standard UFH.[49,50]

Clopidogrel

Clopidogrel, an adenosine diphosphate inhibitor, is mostly utilized as anti-platelet drug. Inhibiting the release of pro-thrombotic and pro-inflammatory mediators, clopidogrel has also several interesting anti-inflammatory properties.[5,51] However, these anti-inflammatory properties, especially in the AMI setting, have never been thoroughly explored.

Glycoprotein IIb/IIIa

Glycoprotein (GP) IIb/IIIa receptor blockade prevents platelet aggregation, but their beneficial effects may extend beyond this platelet inhibitory effect.[52] In fact abciximab, contrary to other small molecular GP IIb/IIIa blockers (e.g.tirofiban), have a high affinity to the MAC-1 receptors. Therefore, it plays an important role in reducing the vascular SMC apoptosis during ischaemic events. Furthermore, by reducing the level of C-reactive protein, IL-6, and CD-40 ligand, abciximab also shows positive anti-inflammatory and cyto-protective effects on suffering myocardial cells.[53]

Insulin

In AMI, insulin treatment improves outcomes not only due to its anti-hyperglycaemic effects, but also due to its anti-inflammatory and pro-fibrinolytic properties. Insulin, with its vasodilatatory and anti-platelets effects, may also improve the micro-vessel perfusion with significant benefit on the post-ischaemic CK and C-reactive protein level.[54,55]

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In human tested novel compounds

Complement cascade inhibitors

MI activates the complement system in animal models as well as in humans. To stop the activation of the complement system, many strategies have been proposed in the experimental setting: depletion of the complement factors (e.g. cobra venimon);[56] monoclonal antibodies directed against complement factors;[57] specific C1 receptor injection;[58,59] selective inhibition of the C5a factor.[60,61]

In animal models, inhibition of the C5a factor has diminished reperfusion injury resulting in a decreased infarction extension.[60,61]

Following these encouraging preliminary animal results, several human trials have been recently performed.

In the COMMA trial, a selective inhibition of the C5a factor with pexelizumab associated with a mechanical reperfusion strategy (i.e. primary PCI) did reduce neither the post-ischaemic CK blood level nor the MI size. However, at 90 days, the all-cause mortality was significantly reduced in the active treatment group.[62]

The COMPLY trial utilizing the same molecule associated with systemic thrombolysis in patients presenting with an AMI did not show any clinical benefit at follow-up.[63] Similar negative results were observed in the PRIMO-CABG trial, where the composite outcomes, utilizing pexelizumab in patients undergoing surgical myocardial revascularization (CABG), were worse in the active treatment group. These results were attributed to a probable over-stimulation of the complement system caused by the extra-corporal circulation utilized for the on-pump CABG procedures.[64,65]

Because of the positive impact on mortality observed with pexelizumab in the COMMA trial, a similar larger mortality study combining this selective inhibition of C5a associated with primary PCI is underway and will provide some interesting new evidence on the efficacy of this treatment modality in the AMI setting (APEX-AMI trial).[66]

Antibodies

Monoclonal antibodies against CD11b as well as antibodies against CD18, which theoretically diminish vascular leucocyte adhesion, showed neither MI size reduction in dog (against CD11b),[67] nor a significant benefit in human trials (against CD18).[68]

Adenosine agonist

The A1–A2 adenosine agonists AMP-579[69] and ATL 146[70] stimulate the myocardial ischaemic pre-conditioning, diminishing the MI size in animal models. In the AMISTAD trial, adenosine agonists associated with a systemic thrombolytic therapy in patients presenting an AMI showed a reduction of the MI size.[71] However, these positive effects were thereafter surprisingly not confirmed in the ADMIRE trial, where adenosine agonists administration after primary PCI did not result beneficial.[69]

In animal tested novel compounds

Anti-TNF-α

Both TNF-α and IL-6 molecules are implicated in the early systemic and loco-regional inflammatory response and shown to have negative effects especially on ischaemic myocardial cells. Anti-TNF agents block the interaction between TNF and its receptors on the endothelium leading to a significant benefit in the early post-ischaemic myocardial repair of the rat.[72]

CI-959

This synthetic molecule is a cell-activator inhibitor, which diminishes the free radical production of inflammatory cells and has shown promising efficacy limiting MI size in the dog model.[73]

Methotrexate

The anti-inflammatory properties of methotrexate are related to an adenosine degradation inhibition at the inflamed site, limiting, in the dog model, the post-ischaemic inflammation process and the MI size.[74]

IL-1 antagonist

IL-1 plays an important role in the ischaemic/reperfusion myocardial damage. In the rabbit model, its inhibition showed preliminary promising results, which need further confirmation in human clinical trials.[75]

Phosphodiesterase IV inhibition

Rolipram, a phosphodiesterase IV inhibitor, increases the intracellular c-AMP and diminishes the inflammatory response of the ischaemic myocardium, limiting the size of the necrosis in the dog model.[72]

Frizzled A

Frizzled A is a recently discovered protein produced in cardiomyocytes and endothelial cells which by inducing angio-neogenesis has shown to reduce the inflammatory response and the MI size in the mice model. These results suggest that this protein may also be interesting in patient presenting diffuse CAD not suitable for percutaneous or surgical revascularization.[7]

Recombinant human erythropoietin

Recombinant human erythropoietin protects the myocardium from the ischaemic-reperfusion injury promoting a positive remodelling in the rat model. This phenomenon suggests that this molecule may also be successfully utilized in humans.[76]

Systemic vs. local delivery

During and after an AMI, both systemic and loco-regional inflammation may worsen clinical outcomes. To control these pathological reactions, anti-inflammatory drugs may be administrated systemically or locally.

Site-specific molecules administrated via a catheter allow to achieve a higher regional drug concentrations,

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with much lower doses of drugs, thereby containing systemic side effects.[77–83]

However, this modality of administration is a 'single shot' option limited to the time of direct PCI. Therefore, if a prolonged treatment would be needed, systemic administration should take over.

Conclusions

Myocardial ischaemia, and especially MI leads to a systemic, as well as to a loco-regional inflammatory response. This inflammation aims to promote a physiological complex myocardial healing process.

Nowadays, several reports suggest that the inflammation in itself may paradoxically have deleterious effects on myocardial cells, especially in the case of an exuberant inflammatory response.

Through the inhibition of the humoral and the cellular pathways, inflammation has been for many years a pharmacological therapeutic target in animal models, with very encouraging preliminary results. Nevertheless, the so far utilized compounds and treatment strategies did not find, to these days, any clinical impact, confirming that more efforts need to be performed to better understand the complex inflammatory response triggered by myocardial ischaemia.

However, in view of many encouraging experimental data, the combination of available and new anti-inflammatory treatments, systemically or locally applied, associated with primary PCI as reperfusion strategy, is likely to become the treatment of choice of AMI in the near future.

Conflict of interest: none declared.

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