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Review

Modulation of the monocyte/macrophage system in heart failure by targeting heme oxygenase-1☆

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ABSTRACT

Upon myocardial infarction (MI) immune system becomes activated by extensive necrosis of cardiomyocytes releasing intracellular molecules called damage-associated molecular patterns. Overactive and prolonged immune responses are likely to be responsible for heart failure development and progression in patients surviving the ischemic episode. Heme oxygenase-1 (HO-1) plays a crucial role in heme degradation and in this way releases carbon monoxide, free iron, and biliverdin. This stress-inducible enzyme is induced by various oxidative and inflammatory signals. Consequently, biological actions of HO-1 are not limited to degradation of a toxic heme released from hemoproteins, but also provide an adaptive cellular response against chronic inflammation and oxidative injury. Indeed, the immunomodulatory and anti-inflammatory properties of HO-1 were demonstrated in several experimental studies, as well as in human cases of genetic HO-1 deficiency. HO-1 was shown to suppress the production, myocardial infiltration and inflammatory properties of monocytes and macrophages what resulted in limitation of post-MI cardiac damage. This review specifically addresses the role of HO-1, heme and its degradation products in macrophage biology and post-ischemic cardiac repair. A more complete understanding of these mechanisms is essential to develop new therapeutic approaches.

1. Introduction

During past 40 years, mortality rate caused by cardiovascular diseases (CVD) decreased significantly. Nevertheless, CVDs are still the primary cause of death worldwide. Disruption of myocardial blood supply, caused by atherosclerosis or thromboembolism, leads to ischemia, myocardial infarction (MI), heart failure (HF) and even death [1]. Following MI, phagocytes (neutrophils and monocytes/macrophages) clear the necrotic tissue by removing dead cardiomyocytes and their released content. Hence MI, the prevalent cause of HF [2], is inevitably associated with immune responses, which are involved in cardiac remodeling (changes in size, shape, structure and function), as well as maintenance of its integrity, healing and preservation of contractile function (reviewed in [3]). Inflammation is generally considered a protective reaction facilitating a recovery process at the site of injury. However, preliminary evidence indicates that an excessive and prolonged proinflammatory response following MI may evoke necrosis of surviving cardiomyocytes, or elicit an exaggerated extracellular matrix degradation, resulting in excessive infarct expansion, adverse cardiac remodeling and HF development. Unfortunately, a number of therapeutic approaches designed to target the proinflammatory response following MI failed to reduce MI size or improve clinical outcomes (reviewed in: [4]). Therefore, a better understanding of the mechanisms governing timely resolution of inflammation seems to be crucial for novel and effective therapeutic strategies design.

Heme oxygenase (HO) is a key enzyme involved in heme catabolism and recycling of heme iron. HO was described for the first time in 1968 as a microsomal enzyme which catalyzes the oxidation of heme and its breakdown into a bile pigment, bilirubin [5]. Soon, this enzymatic activity involving several redox reactions was characterized. The reaction of heme oxidation by HO has an absolute and stoichiometric requirement for molecular oxygen (O_2) and NADPH. It also requires the

Abbreviations: AAV, adeno-associated virus; BvR, biliverdin reductase; CO, carbon monoxide; DAMP, damage-associated molecular pattern; Hb, hemoglobin; HF, heart failure; HO, heme oxygenase; Hp, haptoglobin; Hx, hemopexin; I/R, ischemia-reperfusion; LV, left ventricle; Mb, myoglobin; MDMs, monocyte-derived macrophages; MI, myocardial infarction; PRR, pattern recognition receptor; ROS, reactive oxygen species; TLR, toll-like receptor

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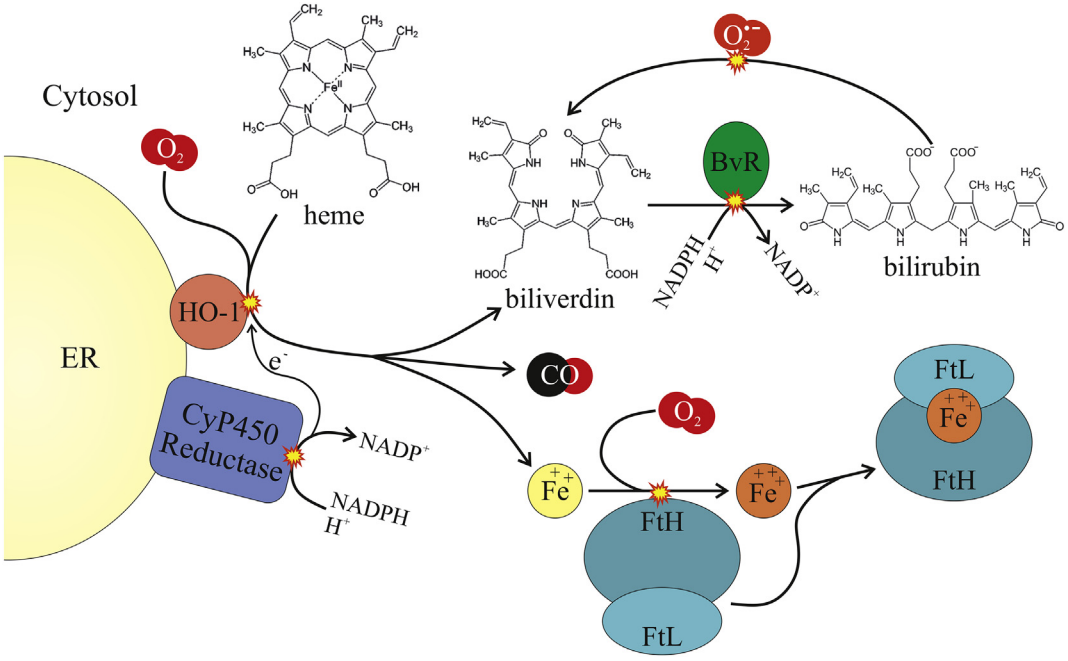

Fig. 1. Schematic representation of reactions involved in heme catabolism. ER – endoplasmic reticulum, HO-1 – heme oxygenase-1, CyP450 Reductase – cytochrome P450 reductase, FtH – ferritin heavy chain, FtL – ferritin light chain, BvR – biliverdin reductase.

participation of cytochrome P450 reductase (CyP450R) activity. As a result of its action stoichiometric amounts of carbon monoxide (CO), ferrous iron (Fe^{2+}) and biliverdin are generated. The latter one is then converted into bilirubin by biliverdin reductase (BvR) present in the cytosol [6] (Fig. 1). In fact, the reaction catalyzed by HOs involves seven steps and is rate-limiting part of heme catabolism [7].

HOs can be found in both plants and animals and they are evolutionarily conserved proteins [8]. There are two HO isoenzymes: inducible heme oxygenase-1 (HO-1) and constitutive heme oxygenase-2 (HO-2) encoded by different genes [9,10]. Biosynthesis of a stress-inducible HO-1 can be triggered by a variety of stimuli, such as its substrate free heme, hypoxia (in rodents), cobalt protoporphyrin, heat shock, proinflammatory cytokines, hydrogen peroxide, nitric oxide and others (reviewed in [11]). Basal levels of HO-1 in mammalian tissues seem to be very low, excluding spleen. This organ is a major site of iron recycling from hemoglobin (Hb) of senescent erythrocytes phagocyted by macrophages [9,12]. Up to date, there were only two described cases of human HO-1 deficiency. One was characterized by constant, severe endothelial damage, elevated von Willebrand factor and thrombomodulin causing abnormalities in coagulation and fibrinolysis system [13]. The other suffered from congenital asplenia, severe hemolysis, inflammation and nephritis [14]. The facts that there were only two cases of HO-1 deficiency reported and the consequences were deadly, suggest that expression of HO-1 is crucial in human physiology, including proper functioning of the cardiovascular system.

This review will summarize the mechanisms of immune responses following MI with special emphasis on the role of different subsets of cardiac macrophages in these processes. We will also discuss the participation of HO-1 and its activity products in the resolution of inflammation, making this protein an interesting molecular target for pharmacological and genetic manipulation in CVD.

2. Role of HO-1 in macrophage biology – from heme uptake to macrophage polarization

Macrophages are specialized in iron recycling with increased expression of proteins for heme acquisition and its breakdown, iron storage and its export [15]. Thus, HO-1 was suggested to be crucial for a proper maintenance and function of macrophages, which can provide fast detoxification of heme released from damaged cells during MI. Accordingly, cardiac macrophages were reported to express high levels of HO-1 [16]. Both Hb and free heme are highly cytotoxic due to their very potent oxidative properties. Because of the presence of ferrous iron, via Fenton chemistry reactions, they take part in the generation of reactive oxygen species (ROS), what results in lipid peroxidation and cell death [17,18]. To prevent such deleterious effects, Hb and free heme have to be scavenged and subsequently degraded. In macrophages, several receptors are responsible for the uptake of heme in different forms. Hb, which after liberation from erythrocytes immediately forms a complex with haptoglobin (Hp), is recognised by CD163 receptor [19] (Fig. 2A). Importantly, this molecule is expressed exclusively in monocytes and macrophages [20] and is strongly associated with their anti-inflammatory phenotype [21,22]. Moreover, it was shown that HO-1 knockout animals do not have CD163-expressing macrophages in the liver and spleens, what results in decreased ability to clear Hb from blood [23].

Apart from Hb oxidation, heme release may be also a result of myoglobin (Mb) or cytochromes breakdown at the site of injury. Labile heme in the circulation is bound by hemopexin (Hx), what allows for CD91-mediated uptake of the complex and later on its degradation [24] (Fig. 2A). Recently, a potential interaction of Mb with Hp was described [16]. Despite the interaction is not as strong as Hb-Hp, removal of Mb-Hp complexes via CD163 scavenger receptor seems to be possible [16]. Interestingly, a CO-mediated arrest of the oxidative activity of Mb [25] indicates another way of preventing Mb-mediated oxidative damage. Regardless of the recognition and internalisation route, heme is then transported from the lysosomes by heme carrier protein 1 (HCP-1) and heme-responsive gene 1 protein (HRG-1) transporters and metabolised by HO-1 in the cytoplasm [26,27] (Fig. 1).

On the other hand, free heme can be considered as a direct inducer of the inflammatory response, as it may function as damage-associated molecular pattern (DAMP). DAMPs, which can activate pattern recognition receptors (PRRs), appear when cells are dying by accidental or regulated necrosis (necroptosis) after ischemic episode and release endogenous material into the extracellular space [1]. Based on the subcellular localization PRRs can be subdivided into two major classes:

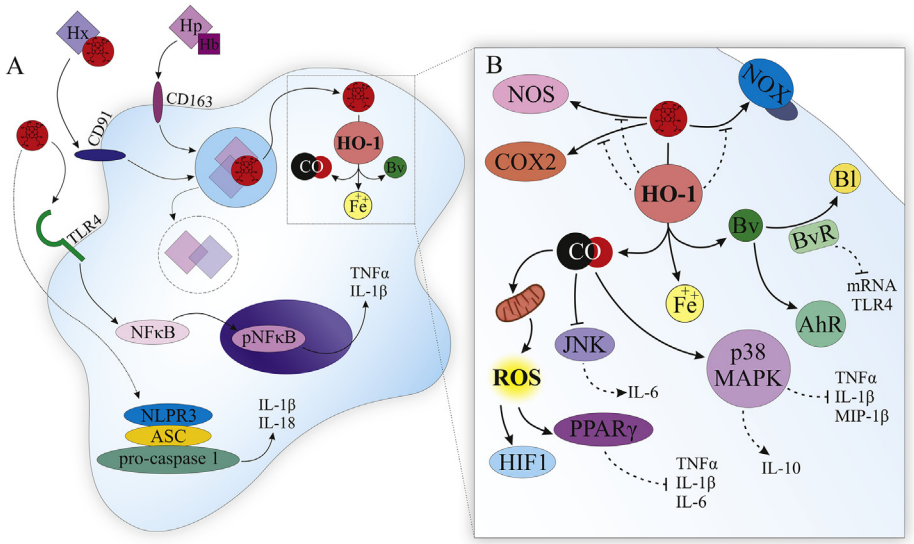

Fig. 2. A) Heme uptake and recognition in macrophages. B) HO-1 effector mechanisms in macrophages. Hb – hemoglobin, Hp – haptoglobin, Hx – hemopexin, ASC – apoptosis-associated speck-like protein containing a caspase recruitment domain, Bv – biliverdin, BvR – biliverdin reductase, Bl – bilirubin, Ft – ferritin, HIF1 – hypoxia inducible factor 1, PPARγ – Peroxisome proliferator-activated receptor γ, ROS – reactive oxygen species, AhR – aryl hydrocarbon receptor, NOX – NAD(P)H oxidase, COX2-cyclooxygenase 2, NOS – nitric oxide synthase, MAPK – mitogen-activated protein kinase, JNK - c-Jun N-terminal kinase.

1) located on plasma membranes or in endosomes: toll-like receptors (TLRs) and C-type lectin receptors; 2) residing in intracellular compartments: retinoic-acid inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors (NLRs) and absent-in-melanoma 2 (AIM2) receptors [28]. It was demonstrated that heme binds toll-like receptor 4 (TLR4) in a way distinct from previously established for lipopolysaccharide (LPS) – a classical TLR4 ligand, leading to tumor necrosis factor α (TNFα) production in macrophages [29,30] (Fig. 2A). Additionally, heme can act synergistically with agonists of TLR2, TLR3, TLR9, as well as cytoplasmic NOD1 and NOD2 receptors [31]. We have recently demonstrated that overexpression of HO-1 in a mouse skeletal muscle damaged by femoral artery ligation decreases ischemia-induced expression of TLR4 and TLR9 and diminishes TLR-triggered inflammation [32], what could be related to more efficient removal of heme, which acts as DAMP at the site of injury. Besides PRRs, recent studies have shown that heme is also sensed by the nucleotide-binding domain leucine-rich repeat-containing receptor, pyrin domain-containing 3 (NLRP3) inflammasome, thus regulating interleukin 1β (IL-1β) and interleukin 18 (IL-18) maturation and secretion [33] (Fig. 2A).

An important aspect of macrophage biology, highly influenced by HO-1 activity, is macrophage polarization. The broadest classification, based on the *in vitro* stimulation, surface marker expression, and inflammatory cytokines production, describes macrophages as classically activated, proinflammatory (M1) and alternatively activated, anti-inflammatory, associated with tissue repair (M2) [34] (Table 1). Unfortunately, such simplification reflects neither the complex *in vivo* microenvironment nor the real diversity of macrophage populations. Although several types of macrophages were distinguished (including M2 subtypes, hemorrhage-associated, generated with oxidized lipids and M4, Table 1), assignment of these cells to a specific subgroup undoubtedly still remains challenging [35,36]. In general, differentiation towards anti-inflammatory phenotype is associated with increased heme catabolism by HO-1 and iron retention by ferritin together with upregulation of CD163 expression [37]. Such properties are also relevant for cardiac resident macrophages [38] and their more detailed characteristics is described below in this review. Importantly, it was demonstrated that polarization towards an M2 phenotype can be achieved through exposure of human macrophages to apoptotic cells and the mechanism involves upregulation of HO-1 by sphingosine-1-phosphate derived from cells undergoing apoptosis [39]. Furthermore, in some experimental models, the M2 phenotype was linked to induction of HO-1 expression in macrophages by hemin and adiponectin (reviewed in: [40]).

3. Role of HO activity products in modulation of inflammation

At first, HO-1 was regarded as an enzyme pivotal for heme catabolism and iron recirculation. However, throughout the years, HO-1 has also been described as an enzyme exhibiting significant anti-inflammatory, anti-oxidant and cytoprotective properties [41]. These effects derive not only from regulation of heme-iron homeostasis, but are exerted also by heme catabolism end products – CO and biliverdin [42–44].

In 1949, a constant production of carbon monoxide in human was reported. What is more, increased production of CO correlated with the abnormal decomposition of erythrocytes [45]. Almost twenty years later increased CO production was observed in patients suffering from hemolytic anemia [46]. The mystery was finally unraveled when the activity of HO, responsible for generation of CO, was described. CO is a

Table 1
Human and murine macrophage subsets based on the in vitro stimuli [35,36,154–157].

Macrophage Subset		Species	Stimulant	Function
M1		mouse, human	TNFα, IFNγ + LPS	Th1 response induction, pathogen clearance
M2	M2a	mouse, human	IL-4, IL-13	Th2 response induction, tissue repair
	M2b	mouse, human	immune complexes, LPS, IL-1β	Th2 response induction, immunoregulation
	M2c	mouse, human	IL-10, TGFβ, glucocorticoids	matrix deposition, tissue repair and remodeling
	M2d	mouse	TLR + adenosine A_{2A} receptor agonists, IL-6	stimulation of angiogenesis
Atherosclerosis-associated	M4	human	CXCL4	proatherogenic, weak phagocytosis
	Mox	mouse	oxidized LDL	proatherogenic, weak phagocytosis
	Mhem	mouse, human	heme	atheroprotective
	M(Hb)	human	hemoglobin, haptoglobin	atheroprotective, cholesterol efflux
	HA-mac	human	hemoglobin, hapotglobin	hemoglobin clearance

signaling molecule involved in many biological processes. Early studies revealed that CO in some aspects is similar to nitric oxide since it was recognized as a neurotransmitter as well [47]. They both are able to activate soluble guanylyl cyclase (sGC), which subsequently generates cyclic GMP [48]. This results in suppression of apoptosis [44], blood vessel relaxation [49], decreased adhesion of leukocytes [50] and inhibition of platelet aggregation [51]. Although CO is mostly associated with its toxicity related to inhibition of O_2 binding to ferrous iron in Hb, such ability to interact with hemoproteins is critical for cell signalling during inflammation [52,53]. Through binding to heme a_3 of cytochrome c oxidase in the respiratory chain, it contributes to the reduction of mitochondrial electron transport and therefore increase in ROS production [54] (Fig. 2B). In this case, rapid burst of ROS enables upregulation of peroxisome proliferator-activated receptor γ (PPARγ) – nuclear hormone receptor, which mediates expression of numerous genes involved in immune responses. In macrophages PPARγ downregulates proinflammatory cytokines including TNFα, IL-1β and IL-6 [55] (Fig. 2B). CO may influence the generation of new blood vessels, as it induces biosynthesis of vascular endothelial growth factor, a potent activator of angiogenesis [51,56]. Moreover, CO is also involved in stromal cell-derived factor-1-driven angiogenesis [57] and may stimulate proliferation of endothelial cells (ECs) [58,59].

What is more, CO can modulate mitogen-activated protein kinase (MAPK) signal transduction, as it was shown to affect both p38 MAPK and c-Jun N-terminal kinase (JNK) pathways (Fig. 2B). In macrophages, CO contributed to reduced JNK phosphorylation and thus attenuated IL-6 production [60] (Fig. 2B). Upon LPS stimulation, CO acts through p38 MAPK pathway [61]. It dampens inflammatory signalling due to inhibition of TNFα, IL-1β, macrophage inflammatory protein-1β (MIP-1β) expression and upregulation of anti-inflammatory interleukin-10 (IL-10) [61] (Fig. 2B). This cytokine is a part of the so-called positive feedback loop on HO-1/IL-10 axis. In such situation, CO generated in macrophages by HO-1 promotes IL-10 production while in turn, this interleukin upregulates HO-1 expression through MAPK and signal transducer and activator of transcription 3 (STAT-3) pathways [61–63]. This mechanism allows for significant signal amplification in monocytes/macrophages and consequently resolution of inflammation.

Recently, IL-10 was also identified as an important mediator of collagen deposition in the development of HF [64,65]. It was shown, that this cytokine activates macrophages found in the hearts of mice suffering from diastolic dysfunction in the autocrine manner [64]. In response, specific subset of macrophages increases production of osteopontin, which acts as a paracrine fibroblast activator. Upon such stimulation, cardiac fibroblasts become activated and promote collagen deposition. This leads to myocardial stiffness and HF. Additionally, IL-10 acting directly on macrophages enhances their phagocytic ability [65]. Altogether, IL-10 can contribute to tissue repair by promoting fibrosis and clearance of apoptotic cells. Yet, the significance of HO-1 in IL-10-mediated actions of macrophages remains to be elucidated.

Biliverdin, another product of HO activity is rapidly converted to bilirubin by BvR (Fig. 1). Primarily, biliverdin and bilirubin were considered as heme degradation waste products, however, these bile pigments possess compelling antioxidative and anti-inflammatory properties [42]. They protect proteins and lipids from peroxidation. Bilirubin acts as a singlet oxygen, superoxide anion or hydroxyl radical scavenger and this action is associated with recovery of biliverdin [66] (Fig. 1). Apart from very potent antioxidative properties, it plays an important role in inhibition of complement activation and T-cell proliferation [67–69]. It also decreases P- and E-selectin expression on ECs which results in attenuation of leukocyte rolling [70]. Biliverdin contributes to downregulation of TLR4 expression in macrophages (Fig. 2B) via direct binding of BvR to TLR4 promoter [71]. Additionally, biliverdin is sensed by aryl hydrocarbon receptor (AhR), which is a transcription factor mediating macrophage activation [72,73] (Fig. 2B). AhR nuclear translocation is induced by binding of tryptophan metabolism products generated by heme-containing dioxygenases: indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase [74]. Thus, the activity of these enzymes may be affected by another HO activity product – CO, which can bind to heme ferrous iron [53].

On the other hand, heme degradation *per se* decreases its availability for the synthesis of hemoproteins and possibly impair their maturation [43]. Such effect was demonstrated for cyclooxygenase-2 (COX2) and nitric oxide synthase (NOS), as after HO-1-induced heme depletion their expression and activity are reduced [75,76] (Fig. 2B). Another important example is NAD(P)H oxidase (NOX), an enzyme crucial for macrophage effector functions. NOX is responsible for superoxide anion production which, apart from its classical role in killing pathogens, is involved in regulation of expression of redox-sensitive genes [77]. Since heme is a component of gp91phox NOX subunit, restriction of its availability by HO-1 may influence not only ROS generation but also downstream signalling pathways [78]. Indeed, recently it was demonstrated that in circulating monocytes HO-1 expression negatively correlates with ROS formation in the aortas of mice, as well as with expression and activity of NOX2 [79].

While heme degradation products have a very broad range of immunomodulatory properties, HO-1 protein itself may interfere with TLR3 and TLR4 signalling. For these TLRs, transduction of signal involves TIR domain-containing adaptor-inducing interferon β (TRIF) and interferon regulatory factor 3 (IRF3). It was demonstrated that in HO-1-deficient macrophages IRF3 nuclear accumulation was reduced affecting IRF3 target genes expression such as interferon β, RANTES, interferon gamma-induced protein 10 (IP-10) and monocyte chemoattractant protein 1 (MCP-1) and suggesting a direct interaction between HO-1 and IRF-3 [80]. In fact, HO is anchored in the endoplasmic reticulum (ER) with its hydrophobic C-terminus, facing the cytosol [81]. Oxidative stress, such as hypoxia, leads to signal peptide peptidase (SPP)-mediated intermembrane cleavage of HO-1 at the C-terminus and its release to the cytosol [82]. Truncated HO-1 loses its enzymatic activity and may be translocated to the nucleus and act as a modulator of transcription factors [83]. Interestingly, as HO-1 is not a traditional transcription factor with DNA binding motifs, rather an indirect transcriptional activation is more likely to occur [84].

4. Regulation of HO-1 expression under conditions of ischemic cardiac damage

Heart is a vital organ with high metabolic demand, rich in mitochondria and it is very vulnerable to oxidative damage [85]. Disruption in coronary blood flow following MI leads to hypoxia (a reduction in the amount of available oxygen) which produces excessive amounts of free radicals and causes ischemic heart disease. If the damage in the ischemic muscle is not repaired, a chronic inflammatory response is set in motion. Chronic inflammation is the hallmark of the ischemic heart disease and is associated with increased oxidative stress and enhanced risk of HF development [86].

Several transcription factors activated under these conditions can upregulate HO-1 and, in fact, the expression of HO-1 is regulated mainly at the level of transcription [11,87,88]. There is a number of transcription factors binding sites located in and upstream of the HO-1 promoter, including nuclear factor E2-related factor-2 (Nrf2), AP-1, and NFκB and their binding activates HO-1 transcription [89]. The HO-1 promoter contains also multiple other positive regulatory elements, such as stress-responsive element (StRE), cadmium-responsive element (CdRE), SMAD-binding element (SBE), AP-2, STATx and upstream stimulatory factor (USF) (reviewed in [11]). Although several transcription factors and signaling cascades are involved in HO-1 regulation, there are two main pathways identified in monocytes and macrophages. One is the already mentioned IL-10/HO-1 axis and the other – Nrf2/Bach1 system.

Nrf2 is one of the key activators of genes involved in the antioxidative response, such as glutathione S-transferase (GST), γ-glutamylcysteine synthetase (γ GCS) and HO-1 [90]. With no stress stimuli,

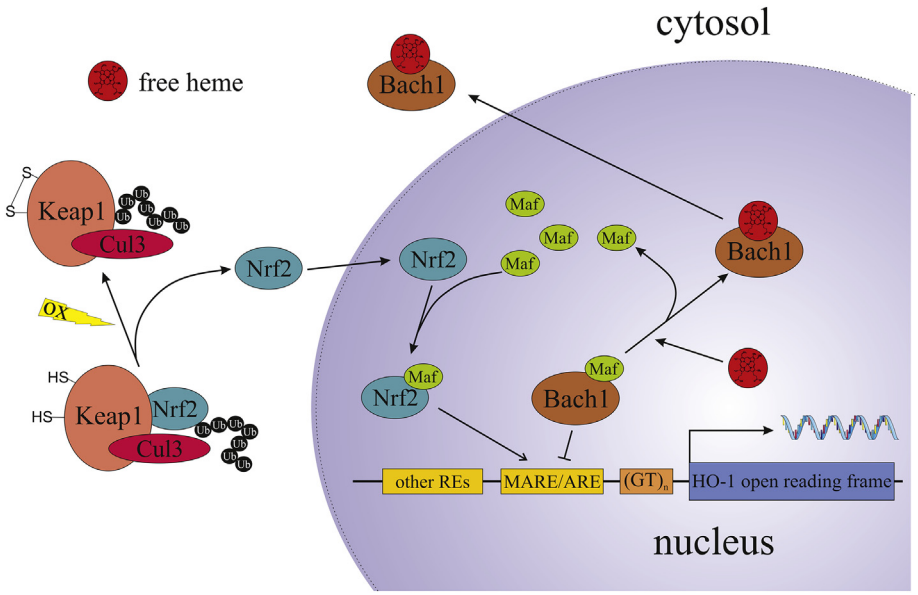

Fig. 3. Regulation of HO-1 expression by selected agents. Upon oxidative modification of Keap1 Nrf2 is released and no longer ubiquitinated by Cul3. After translocation to the nucleus, Nrf2 forms a heterodimer with Maf protein and activates HO-1 expression via antioxidant response element (ARE). Bach1-Maf dimer represses expression of HO-1. Free heme is strongly bound by Bach1. This results in release of Maf, nuclear export of Bach1 and de-repression of HO-1 expression. In human, $(GT)_n$ dinucleotide length polymorphism of HO-1 promoter also affects HO-1 expression. REs – regulatory elements.

Nrf2 is accumulated in the cytosol, bound to Kelch-like ECH-associated protein-1 (Keap1). The protein partner halts Nrf2 translocation to the nucleus and directs it to ubiquitin ligase complex containing Cul3. This results in destining of Nrf2 for proteasomal degradation through conjugation of ubiquitin [91]. However, multiple cysteine residues of Keap1 are prone to oxidative modifications [92], leading to conformational changes of Keap1 and release of Nrf2 and its nuclear translocation [93]. Then, in the nucleus, Nrf2 binds to the small Maf protein and activates antioxidant response element (ARE), inducing expression of HO-1 [91] (Fig. 3). On the other hand, heme-regulated transcription repressor Bach1 binds Maf proteins and thus represses HO-1 via Maf response element (MARE). In this way, Bach1 also competes with Nrf2 for binding of Maf proteins [94]. Interestingly, heme can be bound by Bach1 with high affinity and may restrict the interaction of Bach1 with MARE [95] (Fig. 3). Thus, heme abolishes Bach1-mediated repression of HO-1 transcription. Importantly, numerous data indicate that HO-1 induced through Nrf2/ARE signaling pathway (either pharmacologically or genetically) confers tissue protection via decreasing oxidative stress and inflammation (reviewed in: [96]]. This may be useful in the clinical perspective.

Another aspect of regulation of HO-1 expression in human cells is $(GT)_n$ dinucleotide length polymorphism of the promoter. Amongst human population, both basal and induced levels of HO-1 may vary. The human HO-1 promoter contains from 12 to 40 GT repeats, located approximately 250 bp upstream of the site where transcription of the gene starts (reviewed in: [97]). The most frequently described variants contain 23 and 30 repeats in different study populations (reviewed in: [97]). The more $(GT)_n$ repeats are found in the promoter, the more HO-1 expression is decreased [98]. Such a variant found in monocytes is associated with higher risk of arterial hypertension and decreased cumulative survival [79].

5. Spatiotemporal kinetics of monocyte/macrophage infiltration of heart after myocardial infarction

Shortly after MI, different cells participate in the development of sterile inflammation (in absence of pathogens) in affected tissue. Cardiac macrophages residing in the myocardium provide a primary innate immune response triggered by activation of PRRs by DAMPs [99]. PRRs further activate IRF-, NFκB- and AP-1-signalling pathways and evoke production of interferons and proinflammatory cytokines in the injured heart [99]. Interestingly, very recently a novel PRR – cGAS (cyclic GMP-AMP synthase) sensing cytosolic DNA, has been identified as being potently activated in macrophages following MI. Such cGAS activation triggers STING (stimulator of interferon genes) cascade and promotes the transformation of macrophages toward inflammatory M1-like phenotype [100]. Inactivation of the pathway leads to change of macrophage polarization toward M2-like, reparative phenotype, improving wound healing and angiogenesis, as well as decreasing pathological cardiac remodeling, preventing ventricular rupture, and markedly enhanced survival after MI [100].

The first wave of cells infiltrating heart shortly after MI is composed mainly of neutrophils, with the highest number on the first day after ischemic episode [101]. These cells are recruited via C-X-C motif chemokine ligand-2 (CXCL-2)- and CXCL-5-mediated chemotaxis. Both chemokines are produced by cardiac macrophages [102]. Neutrophils are followed by monocytes. In mice, there are two main subsets of monocytes that differ in expression of Ly6C and CD43. Classical monocytes are described as $Ly6C^{high}$ $CD43^{low}$ and regarded as inflammatory. They are able to enter the damaged or inflamed tissue and differentiate into macrophages. This process of migration is mainly driven by CCR2-monocyte chemoattractant protein-1 (MCP-1, CCL2) axis, as CCR2 is strongly expressed by classical monocytes [3]. Additionally, classical monocytes may transdifferentiate into nonclassical $Ly6C^{low}$ $CD43^{high}$ monocytes which do not express CCR2. Nonclassical monocytes patrol the intravascular endothelial cell surface and clear dying endothelial cells [3,103]. Sometimes a third intermediate population is distinguished and characterized by high expression of both Ly6C and CD43 [104]. In humans, there are at least 3 subsets of monocytes: $CD14^{high}$ $CD16^{-}$ similar to murine classical monocytes, proinflammatory $CD14^{high}$ $CD16^{+}$, and $CD14+CD16^{high}$ similar to murine nonclassical monocytes [105]. Monocytes may be recruited to ischemic tissue even 30 minutes following MI [101] and within few days they differentiate into macrophages, exhibiting reparative phenotype [106]. In the later chronic phase of inflammation, macrophages are maintained, again, by local proliferation rather than further monocyte recruitment [107].

Importantly, monocytes invading ischemic myocardium are not solely generated in bone marrow, but also in extramedullary sites, such as spleen [108]. It was reported, that around 40% of $Ly6C^{high}$ monocytes found in the myocardium after MI are of splenic origin [109]. Moreover, studies have shown that generation of monocytes in spleen in response to MI may contribute to the acceleration of atherosclerosis [110]. Interestingly, HO-1 expression is linked to the number of $Ly6C^{high}$ monocytes. Hinkel et al. demonstrated that the influx of immune cells, including $Ly6C^{high}$ monocytes, to the ischemic heart is

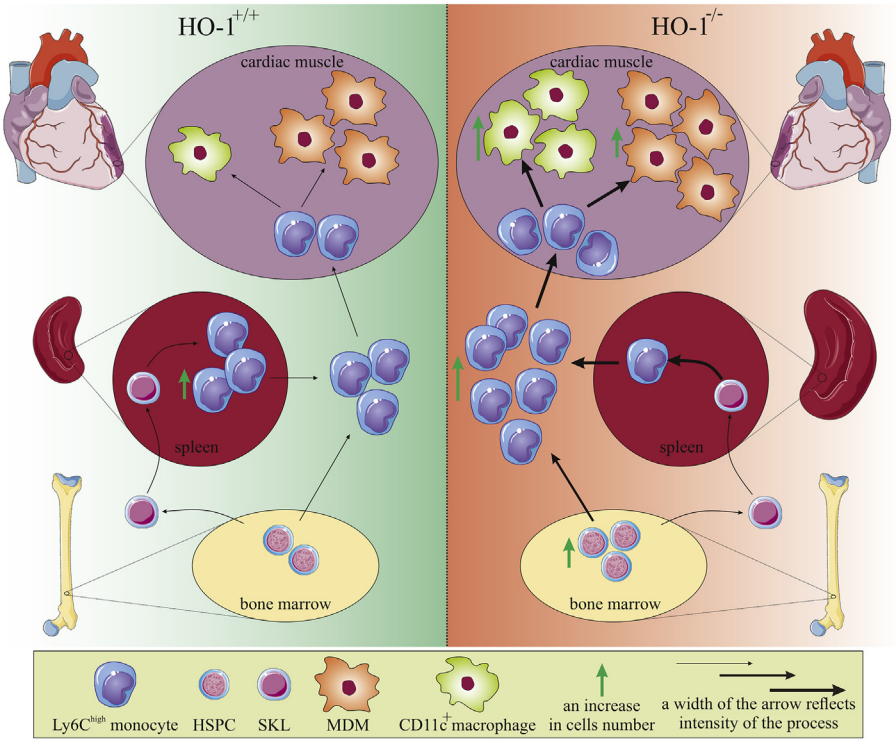

Fig. 4. Monocytopoiesis in the bone marrow and spleen following MI in the presence and absence of HO-1. HO-1 knockout (HO-1$^{-/-}$) mice are characterized by higher numbers of hematopoietic stem and progenitor cells (HSPCs) in bone marrow. These cells give rise to, among others, blood monocyte populations. Additionally, SKL (Sca-1$^+$ c-kit$^+$ Lin$^-$) hematopoietic cells released from bone marrow home to the spleen, where they are responsible for extramedullary monocytopoiesis and additional generation of proinflammatory Ly6C^{high} monocytes. Spleen usually serves as a reservoir for surplus monocytes, however in HO-1$^{-/-}$ mice majority of monocytes originating from spleen seem to reinforce the peripheral blood pool. Upon MI, monocytes infiltrate cardiac muscle and differentiate there to macrophages. Lack of HO-1 leads to accumulation of higher numbers of macrophages in ischemic cardiac muscle. The difference in spleen size shown in the figure is relevant for HO-1$^{-/-}$ mice at the age of 4 months and older.

exacerbated in the absence of HO-1 [111]. On the other hand, cardiac overexpression of HO-1 with gene therapy was able to revert this process [111]. Our recent findings confirmed these observations. A more potent deterioration of post-MI LV function observed in HO-1 knockout mice was accompanied by higher numbers of Ly6C^{high} monocytes in peripheral blood and greater numbers of proinflammatory macrophages in the heart [103] (Fig. 4), what can be related to the higher expression of adhesion molecules (vascular cell adhesion molecule 1 – VCAM1, intercellular adhesion molecule 1 – ICAM1, E-selectin) in the absence of HO-1. Additionally, we identified spleen as an important source of these cells [103] (Fig. 4). It was recently demonstrated that HO-1 affects granulopoiesis in mice through regulation of myelocyte proliferation accompanied by changes in expression of transcriptionally active C/EBPβ protein [112]. But, the mechanism by which HO-1 regulates the production of monocytes remains to be elucidated.

During past few years, the old model suggesting that tissue macrophages originate from circulating blood monocytes was extensively revised. There is plenty of evidence suggesting that tissue macrophages are of embryonic origin and thanks to *in situ* proliferation they persist into adulthood in the tissue independently of monocytes [113–116]. Interestingly, fate mapping driven by CD115 revealed that yolk-sac derived macrophages persist into adulthood in substantial numbers only in the heart, liver and brain [117]. The same study demonstrated that cardiac tissue macrophages are established during embryonic development, independently of definitive hematopoiesis in the fetal liver. In the adult murine heart there are plenty of macrophage populations. The first one is embryonically established and separates from blood monocytes. These cells do not express CCR2. Among them, there are MHC-II^{low} Ly6C$^-$, MHC-II^{high} Ly6C$^-$ and Ly6C$^+$ subsets (Fig. 5, Table 2). The other population is low in number, derived from blood monocytes and characterized as CCR2$^+$ Ly6C^{high} [117] (Fig. 5, Table 2). Interestingly, neonatal heart contains mainly embryonically established, MHC-II^{low} CCR2$^-$ macrophages [118] (Fig. 5, Table 2). Several studies demonstrated that rodent neonatal heart is able to regenerate after serious damage including apical resection [119], MI [120] or cryoinfarction [121]. What is more, this phenomenon depends on the local expansion of cardiac CCR2$^-$ macrophages of embryonic origin, which are necessary for the regeneration [118,122]. Embryonic-derived macrophages in the injured neonatal heart are able to promote proliferation of cardiomyocytes and stimulate coronary angiogenesis, and simultaneously produce minimal inflammation [118]. Taking into account the proangiogenic and anti-inflammatory properties of HO-1, it would be interesting to investigate the role of HO-1 in neonatal macrophage biology under cardiac damage conditions.

On the other hand, after injury of the adult heart, inflammatory monocytes are abundantly recruited to damaged myocardium and they differentiate into monocyte-derived macrophages (MDMs). They have strong proinflammatory phenotype and very limited capacity to promote angiogenesis and cardiomyocyte proliferation. This loss of regenerative potential in the adult myocardium was also attributed to the loss of CCR2$^-$ and expansion of CCR2$^+$ MDMs [118], as well as to the low proliferative capacity of adult cardiomyocytes, which do not possess regenerative potential like the neonatal ones. Proinflammatory monocytes and MDMs contribute to a loss of tissue-resident macrophages, augment monocyte and neutrophil infiltration and therefore impair LV recovery of the adult heart [118,122]. We have recently shown that in HO-1 deficient mice even 3 weeks following MI monocytosis in peripheral blood was present and populations of cardiac macrophages were strongly enriched in CD11c$^+$ subsets [103] (Fig. 4). Macrophages expressing CD11c were previously reported to represent a classical proinflammatory phenotype and to efficiently produce IL-1β, TNF-α and IFN-γ [123].

6. Pharmacological and genetic manipulation of HO-1 expression in cardiac ischemia

HO-1 is a meaningful player in governing cardiac homeostasis and following cardiac damage. HO-1 expression is strongly induced after MI [103], however, the endogenous induction seems to be either not strong enough or too late to fully pronounce actions of the protein. It was previously shown, that artificially increased levels of HO-1 after MI resulted in improved heart function and lowered infarct size, reduced apoptosis and inflammation [111,124,125]. Furthermore, high expression of HO-1 in atrial fibroblasts abrogated collagen production [126].

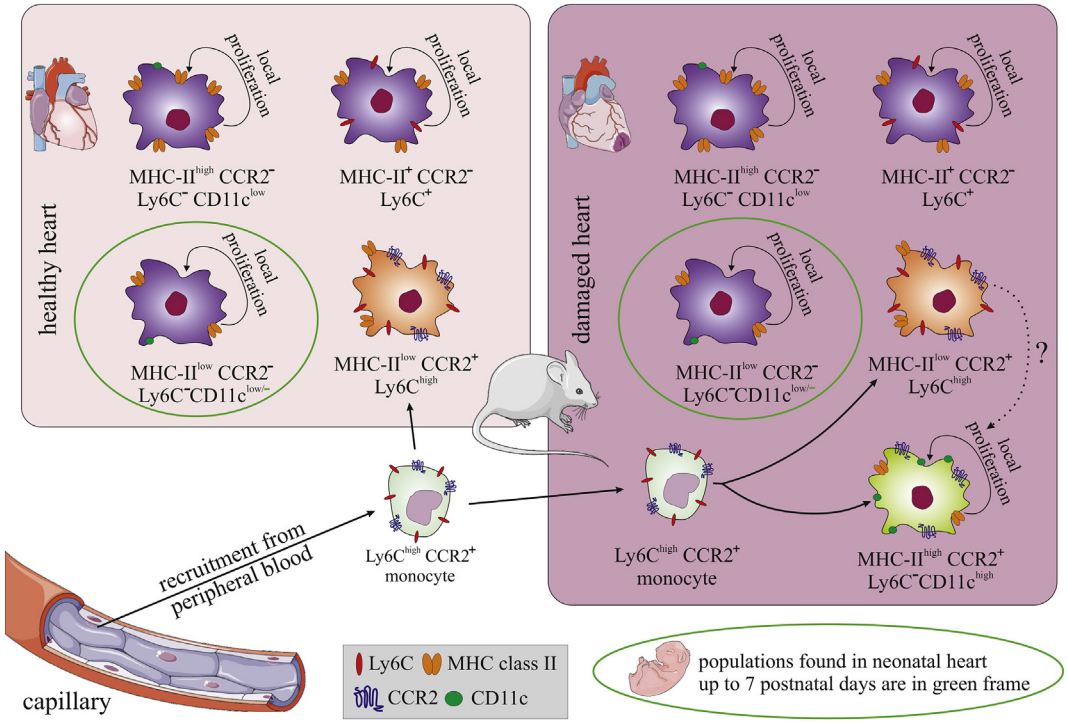

Fig. 5. Cardiac macrophages in adult and neonatal heart in steady-state and after tissue damage. The scheme represents the populations of macrophages found in the heart and does not reflect their abundance and dynamics in the course of cardiac sterile inflammation.

On the other hand, lack of HO-1 *in vivo* was associated with greater than in wild-type mice collagen deposition in atria in steady-state [126] and in LV after MI [103].

Due to high energy demand, cardiomyocytes depend on oxidative respiration [127] and contain numerous mitochondria, which occupy at least 30% of the cell volume [128]. Therefore, the cells contain lots of hemoproteins, such as cytochromes and Mb [129]. Thus, in these cells, heme management is substantial. It may indicate that HO-1 is very important for maintenance of cardiomyocyte homeostasis. It was suggested, that cells, such as cardiomyocytes, overexpressing HO-1 are better prepared for local excessive heme release from dying cells [130]. There are numerous studies demonstrating protective properties of high HO-1 level in cardiomyocytes. Delivery of exogenous HO-1 by gene therapy or activation of Nrf2/HO-1 pathway in stress conditions results in reduced cardiomyocyte apoptosis, better control of post-ischemic inflammation, prevents cardiac dysfunction and improves cardiac recovery following ischemic damage [111,124,125,131,132]. Also, it was demonstrated, that even the use of HO-1 activity product – CO improves cardiac remodeling and healing after MI [133].

Up to date, various studies have demonstrated significant protective properties of HO-1 in ischemia- or ischemia/reperfusion (I/R)-induced heart injury models. In mice exposed to I/R, heterozygous disruption of HO-1 gene resulted in an increase of infarct size, as well as reduced recovery of LV function [134]. We have recently shown that even more pronounced effects could be observed for HO-1 knock-out animals, where MI induction led to severe impairment of heart function [103]. In such situation, lack of HO-1 contributes to adverse late LV remodelling associated with elevated myocardial infiltration of MDMs [103] (Fig. 5). On the other hand, cardiac-restricted HO-1 overexpression, for both *ex vivo* and *in vivo* experiments involving I/R injury, showed a considerable decrease of the infarct region, improved recovery of heart function together with reduced inflammatory cell infiltration and apoptosis [124]. These results create a rationale for further investigation of HO-1 as a therapeutic agent, especially in MI models.

One of the possibilities of HO-1 targeting is gene therapy. So far, the majority of preclinical studies have focused on recombinant adeno-associated viral (rAAV) vectors as DNA carriers. They not only provide stable, long-term transgene expression in non-dividing cells but also have very limited immunogenicity after in vivo administration [135]. In case of MI, it was demonstrated that HO-1 delivery can exert strong

Table 2
Subpopulations of cardiac macrophages in the adult murine heart based on cell surface markers [102,103,118]. * lack of sufficient data to determine the exact function

Macrophage Subset		Origin	Local Proliferation	Properties	Present in steady-state	Function
CCR2$^-$	MHC-II^{high} Ly6C$^-$ CD11c^{low}	embryonic	+	proangiogenic and mitogenic (*ex vivo*)	+	presentation of antigen to T lymphocytes
	MHC-II^{low} Ly6C$^-$ CD11c^{low}	embryonic	+	anti-inflammatory	+	phagocytosis of cell debris
	MHC-II$^+$ Ly6C$^+$	embryonic	+	*	+	*
CCR2$^+$	MHC-II^{low} Ly6C^{high}	monocyte-derived	-	proinflammatory	+	neutrophils recruitment to ischemic tissue, replacement of macrophages of embryonic origin after injury
	MHC-II^{high} Ly6C$^-$ CD11c^{high}	monocyte-derived	+	proinflammatory	-	replacement of macrophages of embryonic origin after injury

cardioprotective effects and therefore be particularly beneficial as a pre-emptive therapy. Administration of rAAV vectors encoding HO-1 several weeks before induction of heart I/R injury resulted in substantial reduction of infarct size, as well as upregulation of anti-apoptotic signalling [136]. In addition, similar conclusions can be drawn also from chronic, recurrent myocardial ischemic injury model, where apart from decreased apoptosis, AAV-mediated HO-1 delivery diminished cardiac fibrosis and inflammatory response [137]. Interestingly, advantageous effects of HO-1 overexpression can be still observed even a year after MI. Long-term studies revealed a significant reduction of mortality together with markedly improved LV function basing on echocardiographic measurements [138]. Moreover, AAV vectors enable very stable and relatively persistent expression of the chosen transgene in heart. Cardioprotective properties of HO-1 could be still noticed, even when MI procedure was performed a year after gene delivery [139]. The promising outcome of preclinical studies in small animals encouraged similar experiments in the porcine model of MI. In this case, administration of rAAV-HO-1 vectors resulted in a considerable decrease of monocyte and neutrophil infiltration with concomitant improvement of LV function [111].

Despite positive results of implemented gene therapy in animal models, there are still many challenges to be overcome prior to starting such treatment of patients. Although many of the experimental procedures involved intramyocardial administration of vectors, such intervention may be very risky in humans. While the systemic administration will be preferable in this case, it also may cause additional adverse effects due to transduction of off-target tissues. This, however, can be at least partially prevented by using regulated expression systems, for example, tissue-specific promoters (MLC2v for heart ventricles), hypoxia-inducible promoters or miRNA-dependent expression constructs [140–142]. Moreover, selection of appropriate AAV serotype of the vector may allow efficient targeting of gene delivery into the heart tissue [143]. Nonetheless, obtaining sufficient level of transgene expression in humans is still one of the most crucial obstacles to successful gene therapy.

Since HO-1 gene delivery methods are not yet available for clinical applications, pharmacological induction of HO-1 expression seems to be a promising alternative. In case of heart I/R injury models, it was demonstrated that pre-treatment of animals with hemin considerably reduced infarct area [144,145]. Of note, this effect was completely reversed after administration of tin protoporphyrin IX (SnPP) – an HO-1 inhibitor [145]. Comparable results were obtained for MI in diabetic mice, where HO-1 expression was induced with cobalt protoporphyrin IX (CoPP). In this study, apart from improved cardiac function, also activation of anti-apoptotic pathways and phosphorylation of glycogen synthase kinase-3 beta (GSK3-β) were observed, thus indicating cardioprotective properties of HO-1 upregulation [146]. Even though these results may be encouraging, possible adverse effects of the application of such HO-1 inducers in patients are still an obstacle. So far, numerous experiments pointed out a very limited specificity of protoporphyrins, together with possible toxicity [147,148]. Another group of compounds that can influence HO-1 level are statins, the inhibitors of hydroxymethyl glutaryl coenzyme A reductase [149]. Due to their anti-inflammatory and pro-angiogenic properties, they were widely studied in terms of cardiovascular diseases. It appears that their beneficial effects can be exerted through HO-1 upregulation mediated by stabilisation of its mRNA via PI3K/Akt pathway [150]. Interestingly, the therapeutic potential of HO-1 induction, to a large extent is comparable to the direct utilisation of heme catabolism end products. Administration of CO (in form of CO-releasing molecule, CORM) resulted in improved post-ischemic heart function recovery, with significantly reduced infarct size and anti-arrhythmic protection [133,151,152]. In case of post-MI treatment, an alternative approach may involve targeting of cardiac macrophages rather than the whole heart. It was recently shown, that lipid-encapsulated hemin can be efficiently delivered to the macrophages what may change their polarization and therefore influence restoration of heart function [153].

7. Conclusions

A better understanding of the pathophysiology of HF is indispensable for the development of new therapies. Numerous data indicate that innate immune cells are crucial for proper infarct healing as they clear the injured zone from dead cells and enable formation of a scar that preserves the structural integrity of the ventricle. However, on the other hand, uncontrolled or excessive inflammatory signals have been implicated in enlargement of the infarct area and HF progression. Thus, in addition to the targeting of specific inflammatory signals, the design of therapeutic strategies needs to take into account important temporal and spatial considerations. Heme released from damaged cells during MI can activate specific receptors and signaling pathways to promote ROS generation, inflammation, and programmed cell death. Hence, its fast removal is indispensable and can be achieved thanks to the activity of HO-1. Several experimental studies demonstrated that overexpression of this enzyme limits post-MI inflammation and infarct area. More selective targeting of HO-1, i.e. in phagocytic cells, by small molecules or genetic approaches may in the future provide a new therapeutic option for patients with cardiovascular complications.

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