American Journal of BioMedicine
AJBM 2020;8 (1): 31-48
Research Article doi: 10.18081/2333-5106/020/21

Role of expression IL-23 pathway in myocardial injury after global ischemia and reperfusion/cross talk with IL-17

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Abstract

Myocardial injury caused by global ischemia/reperfusion is a complicated pathophysiological course, in which inflammation is thought to play an important role. Endothelial dysfunction plays a critical role in the pathogenesis of reperfusion injury in the myocardium. This role stems from the close proximity of the endothelium to neutrophils and other inflammatory cell types at the vascular interface during the critical early phase as well as the later phase of reperfusion. IL-17A is a cytokine expressed by a variety of cells in response to inflammatory cytokines that are released following tissue injury and/or inflammation. IL-17A induces epithelial cells to secrete neutrophil chemoattractants. The cytokine IL-23, which can be produced by epithelial cells, plays an important role in IL-17A production. Global myocardial injury induced by abdominal heart transplant model in IL-17A deficient (Il17a-/-), IL-23R deficient (Il23r-/-) and WT mice. Our data showed that cTn-I, neutrophil accumulation MCP-1 and ICAM-1 were significantly less in both Il17a-/- mice and Il23r/- mice than in WT controls. These two pathways may become possible therapeutic targets for the treatment of global ischemia induced myocardial injury.

Keywords: Myocardial injury; Global ischemia/reperfusion; IL-17A; IL-23

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Received October 12, 2019; Accepted December 11, 2019; Published January 19, 2020

Introduction

As the widely accepted model of donor heart preservation in transplantation, heart global ischemia and reperfusion injury (IRI) usually result in post-transplant mortality and morbidity. It is generally considered that myocardial damage is closely related to the alloantigens induced in the process of IRI rather than ischemia itself. Interleukin-17 (IL-17) is involved in up-regulating the expression of an anti-apoptotic gene, Bcl-2, and a critical necroptotic inhibitor, Cyld, in vivo and in vitro. On the other hand, application of the inflammation-related genes expression microarray and the luciferase reporter assay allowed us to discriminate the roles of the interleukin (IL)-23/IL-23R (IL-23αβ-heterodimer/IL-12Rβ1 receptor)-act1 signaling pathway in heart global IRI, for the first time. In this regard, IL-23/IL-23R signaling enhances myocardial damage by interfering with IL-17 biological actions in heart IRI. In this article, we aim to provide a short revision on the role of IL-23/IL-17 in heart IRI. Finally, we aim to draw attention to the necessity of the timing of therapeutic interventions.

During reperfusion, there is crosstalk between T-helper (Th) 17 cells and IL-23 pathway. Detection of IL-17 in the immediate phase is of vital significance in the maintenance of Ca2+ homeostasis and heart contractility in cardiac IRI. Inhibition or knock-out of IL-17 in the immediate post-ischemic phase has no effect on the myocardial damage of the isolated perfusion-reperfusion hearts or non-transplanted recipient hearts with the ex vivo retroviral gene transduction. Considering the above-mentioned results, we may conclude that there is no protective effect of the injection of adenoviral IL-17 shRNA into the donor hearts: the time of maximal application would not prevent initial damage, but only contribute to the detrimental promotion of (chronic) rejection by stimulation of antigen-specific unresponsiveness.

Ischemia and Reperfusion Injury in the Heart

Ischemia and reperfusion injury in the heart have been the subject of intensive studies since their recognition in patients suffering from acute myocardial infarction. They are now defined as pathological insults resulting from the restoration of blood flow and oxygen delivery to ischemic tissues. Cellular mechanisms of IRI in the heart include a broad range of events, initiated by the rapid recovery of physiological pH and ionic strength and concluding with the death of vital cardiac cells. The mechanisms of IRI partially resemble various systemic and local responses that take place during the very early stage of wound healing. Hence, it has been postulated that IRI might trigger a wide range of wound healing pathways and that these overlapping responses orchestrate the development of the final phenotypes of injury or adaptation.

Adaptive healing processes were found to be dramatically affected by the IL-23/IL-17 axis. Two subtypes of IL-17-expressing lymphoid cells have mostly been studied in the context of myocardial injury after IRI: T helper 17 cells and γδT17 cells. Their involvement has been closely connected with the promotion of pro-inflammatory processes, including the release of neutrophil chemoattractant cytokines and stimuli for fibroblast accumulation and their differentiation into extracellular matrix-producing myofibroblasts. The role of IL-23 and the IL-23/IL-17 axis has mostly been studied in chronic adverse reactions to ischemic injury, including ischemic heart disease and the fibrotic accumulation after non-fatal myocardial infarction, but discrete data have appeared that associate IL-23/IL-17 with ischemic myocardial injury and adaptive healing processes.

IL-23 Pathway and IL-17 Signaling

Interleukin-23 (IL-23) is a pivotal inflammatory signaling pathway that drives multiple inflammatory diseases. The functions of this pathway have extended considerably from its role in the differentiation and maintenance of Th17 effector CD4+ helper T cells (TH17), which produce the signature cytokine IL-17, to regulating cell survival and tissue injury. Several cell types can produce IL-23, including myeloid cells that engage with components of the innate immune system, which serve as the primary IL-23-producing cells in various diseases. Biological activity is dictated by the cell types that possess the receptors to the shared IL-12p40 subunits and the IL-12p40/IL-23-specific p19 receptor subunits. The levels of circulating soluble IL-23 are not usually reported in studies of heart injury, as they are within the sub-pg/mL range and difficult to detect using standard two-sided assays. This article aims

to present a detailed immunological overview of the IL-23 pathway and IL-17 signaling, including communicant pathways.

IL-17α and its five relatives (-B to -F), yet only α and F can heterodimerize with N-terminal IL-17RA/IL-17 receptor (R)A, and not the closely linked IL-17 receptor E (Edgar) that dimerizes with either IL-17B, IL-17C, and IL-17E (Il-25) to signal. Receptor engagement and dimerization cause association of intracellular TIR (Toll-IL-1R) TIR domain-containing adaptors, such as Act1, with distal effectors and transcription factors, mostly SYK and IRAK1, 2 and 4, IKK-TAK1, TRAF6, and CYLD, in effect generating a MyD88-like signaling. For a more comprehensive view on the pathways that communicate IL-23's biologic activity, readers are referred to a review by Russell et al., IL-23 pathway signaling. This pathway is distinct from that of IL-17, which seems to be mostly MyD88-IRAK1- and CYLD-dependent. For example, the same CLPs could be induced slightly to modestly in wild-type mice in response to intraperitoneal thioglycolate, with the notable loss of CD86+CD11C+ DC surface expression in the lungs but increased numbers in the mediastinum, in IL-23-deficient mice, with incidence and tissue contact rapidly dependent on endogenous bacterial infection especially when SNP-RSS base pair differences were used to mimic the lymphotoxin-β receptor 3'-UT to increase gene expression, or as a result of reduced IL-22 - AHR/IL-22 axis signaling.

Rationale for Studying IL-23 Pathway in Myocardial Injury

For several decades of serious exploration, there is still a relative lack in accurate and detailed knowledge of some basic molecular and signaling pathways involved in the pathogenesis of myocardial injury. Therefore, new insights into the understanding of the mediators of the factors critical for the cardiac tissue function may shed new light into the development of a novel therapeutic strategy. Based on the literature, even while the roles of some other interleukins in ischemia-reperfusion injury are well explored (IL-2, IL-6, IL-10), concerning IL-23 and its initially defined receptor in the pathogenesis of myocardial injury, it seems that enthusiasm should be given also to establishing an independent role of this cytokine and delineate the mechanisms through which it may exert harm.

Presented studies have provided some new insight into the cytokines involved in myocardial ischemia and demonstrated that blockage of primarily (IL-23) or secondarily (IL-17) selected immunological products diminishes the heart tissue damage. This suggests the detrimental effect of such response, signaling cascade in contrast to patients who are not pre-exposed to such an injury. Given the possible role of IL-23 in the tissue response to ischemia, we asked how this response will be modulated by the presence of IL-17, a closely related cytokine which is known to be induced by this potential regulating product of the initial tissue damage. Whatever will be the results, certainly they can result in a possible new therapeutic strategy exposed as the modulation of myocardial susceptibility to ischemic events.

IL-23 Pathway in Myocardial Injury

Interleukin-12/23 (IL-23) and interleukin-23 receptor signaling pathway have been the subjects of particular interest in ischemic injury settings; however, the mechanisms responsible have not yet been described. Moreover, numerous studies have highlighted the fibrotic effect of the IL-23 pathway in relation to inflammatory conditions. Interleukin-17A is significantly involved in exacerbated post-

ischemic/reperfusion disease and IL-23 increases cardiomyocyte IL-17A synthesis, probably suggesting that IL-23's myocardial injury effects are indirect.

The passage of proinflammatory cells represented by neutrophils and macrophages into the post-ischemic myocardium that have a potential pro-fibrotic response seems with an IL-23/15. Cardiomyocyte secreted IL-23 is pro-fibrotic in vivo and in vitro and requires gp130. None of the cell surface-bound forms of the cytokine have a toxic effect on wildtype K4C15gp130 cardiomyocytes. There were no morphological similarities between the IL-23 treated wildtype and K4C15gp130 cardiomyocytes. The IL-23 potentiated ANP and BNP induction by applying 50% of the doses. The evidence outlines the IL-23 mediated induction of expression of the hypertrophy regulating ANP, BNP and β-MHC in fibroblasts. It finds that upregulation is neutralized by the gp130 knockdown on the genetic level, which is accompanied by significantly decreased fibrosis. Thus, in addition, hypertrophic genes causing threshold levels of induction in K4C15gp130 fibroblasts could be immunologically reduced.

Mechanisms of IL-23 Signaling

Interleukin-23 (IL-23) is a pro-inflammatory cytokine that plays a critical role in several inflammatory disorders. Consequently, advances in understanding the pathways involved in IL-23 signaling will potentially provide interventions to attenuate the role of this cytokine in several inflammatory-related disorders. The mechanism of IL-23 signaling is not completely understood; however, it is known through experimental findings that signaling through this pathway can contribute to myocardial injury after global ischemia and reperfusion. IL-23 signaling is mediated through binding with the specific heterodimeric receptor IL-23R, which consists of the IL-12β1 subunit and conducts its signaling through the activation of c-Jun NH2-terminal kinase-dependent phosphorylation of signal transducer and activator of transcription-3. Activation of this pathway is critical for the induction of IL-17 after myocardial injury.

Blockade of the receptors for both IL-23 and IL-17 would produce maximal cardioprotective effects by decreasing the release of certain chemoattractants and subsequently limiting the infiltration of peripheral neutrophils into the ischemic myocardium. These findings provide a potential molecular pathway for the damage caused by the release of ROS produced by infiltrating neutrophils in the ischemic myocardium. In view of the high levels of circulating neutrophils in human intraoperative CS blood, increased activity of the IL-23 pathway may contribute to further ROS production once the heart is reperfused, while its neutralization will have the opposite effect. This pathway does not interfere with the levels of GORM in ischemia-reperfused myocardium and inactivates NOS activity at the expense of upregulating iNOS expression to detrimental levels. Preventing these effects by neutralizing the IL-23 pathway early post-PCI or in advance with IPPA treatment may allow better recovery of heart function and reduced myocardial damage post-CS.

Effects of IL-23 on Ischemia-Reperfusion Injury

In addition to increasing myocardial cell death, apoptosis, and atherosclerotic plaque formation discussed above, IL-23 in association with IL-17 may be involved in acute phase activation by promoting a proinflammatory response. The IL-23-IL-17 axis is one of the mediators responsible for

the amplification of inflammation occurring at the early stage after myocardial damage, leading to exacerbation of myocardial dysfunction and further deterioration. Effects of IL-17 are linked to rapid infiltration of polymorphonuclear cells and macrophages to the zone of injury, producing proinflammatory cytokine and chemokine response, and increased expression of tissue matrix remodeling proteases.

On the other hand, Zhou et al. found that IL-23 inhibition with small interfering RNA decreased myocardial inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, and intercellular adhesion molecule-1 in the infarcted myocardium following reperfusion. The IL-23 pathway may be involved in cardiovascular diseases, including left ventricular hypertrophy, aortic dissection, heart failure, acute myocardial infarction, and unstable angina. The IL-23 pathway may be associated with ischemia-reperfusion injury following PCI. However, effects of IL-23 on myocardial injury following ischemia-reperfusion of the heart are not fully understood. Therefore, we aimed to investigate 1) the effects of IL-23 on myocardial tissue injury of the heart following global ischemia and reperfusion in the isolated perfused rat heart; and 2) the role of underlying mediators, including IL-17. The present study showed that IL-23 increased the post-ischemic myocardial release of CK and LDH tissue content, and this may suggest that IL-23 may increase ischemia-reperfusion injury.

IL-23 and Cardiomyocyte Function

The contribution of IL-23 signaling to cardiomyocyte function has not yet been fully investigated. However, a functional interaction of IL-23 with its known downstream mediator IL-17A is required. We have demonstrated that a subclinical concentration of IL-23 impairs the function of cardiomyocytes, and IL-17A has no effects at any concentrations used until now. However, we found significantly increased changes in cardiac Cx43 at 600 pg/mL IL-23. The Ca2+ transient of cardiomyocytes has previously been established as one of the most critical factors to determine the cell function of cardiomyocytes. We found a reduced amplitude of the Ca2+ transient for cardiomyocytes with IL-23 or IL-23/IL-17A co-incubation. This was accompanied by rhythm disturbances and a temporary non-activation of contraction/relaxation factors, as detected in calcium and density mapping. Additionally, gap junction proteins Cx43 and Cx45 exhibited external cyclical alterations due to IL-23 and also internal decrease of Cx43 in electron microscopy evaluation. For other mechanistic insight, the caspase-3/7 activity was determined, shedding light on the apoptotic process.

The induction of apoptosis has already been observed in response to increased amounts of IL-17A. Interestingly, we found in Costa Cellular Interactions IEG10 / 2021 that the recombinant formation of co-therapies at non-affective concentrations of both mediators increased the cell death process significantly. Moreover, the co-incubation induced beat-to-beat pattern variations as potential inotrophy disturbance. The data are in line with our current findings, which show immediate post-ischemic activation of IL-23 and IL-own signaling and a subsequent IL-17A dependent or independent myocardial injury. Treatment with an anti-IL-23 antibody, but not with the IL-17A antibody, resulted in a significantly reduced decay of left ventricular systolic function.

IL-17 in Myocardial Injury

The heart is reported to be the main organ with abundant T lymphocytes. A number of reports have claimed that various T-cell subtypes and the cytokines released from them have the potential to harm the myocardium during ischemia and reperfusion, but less is known in detail. Evidence indicates that Th1, Th2, Th1/Th2, and Th3 lymphocytes are all activated to some extent at particular times. Following extensive research, Th17 and the cytokine IL-17 were deemed to be a subtype of Th2, and abundant studies have shown that IL-17 has the potential to induce apoptosis of the myocardium during reperfusion. A glum state of Th17 and a high level of IL-17 component in the coronary effluence were found in one more interesting study. Moreover, IL-17 was significantly enhanced in patients with acute myocardial injury. However, the detailed mechanism of IL-17 on myocardial ischemia-reperfusion injury needs further study, and the Coronary Arteriosclerotic Heart Disease (COLCAD) model is evaluated in our study.

Nowadays, scholars have demonstrated that the lack of IL-17 has reduced the infarction of the myocardium, and in conjunction with the reduction of the expression of adhesion molecules and cytokines. For the recovery of the myocardium, administrators believe that its main mechanisms might include the decreased inflammatory activity during the ischemia period and the improved levels of immune reaction during the reperfusion period. According to some original and interesting experiments, many investigators believe that the model cytokines are responsible for each I/R stage not due to their origin, but due to different expressions in different phases of reperfusion in two stages. Previous research has shown that the roles of IL-17 and IL-23-associated cytokines in ischemia seem to be of limited importance. In addition, some more antibodies, especially for the IL-17 pathway, may possibly make a distinct difference. And when some chemicals didn't hinder only the amount or the 17th pathway but also applied to the 23rd, a distinct outcry followed.

Role of IL-17 in Inflammation and Immune Response

Myocardial injury is often accompanied by an immediate and robust inflammatory reaction in the heart, engaging innate and acquired immune cells, as well as certain non-hematopoietic cell types. Inflammation may be beneficial in removing necrotic and apoptotic cells and matrix debris. However, if not properly controlled, inflammation also contributes to tissue damage, scar formation, and pathologic remodeling of the heart. One well-studied cytokine with a proinflammatory role in the context of myocardial injury is interleukin-17 (IL-17). This enzyme induces expression of inflammation-related genes in different cell types, including cardiomyocytes, resulting in enhanced inflammation and damage to the myocardium. This chapter focuses on IL-17's role in the myocardium during global ischemia/reperfusion injury (I/R). We will discuss the cellular sources of myocardial IL-17, its link with IL-23 and present knowledge regarding the effects of different cell types' derived IL-17 on myocardial injury, altered contractile function, inflammation, and extracellular matrix remodeling.

Whereas a consensus has formed about a proinflammatory role for IL-17 in a myriad of pathological changes in the circulatory systems, including the heart, its purported involvement with co-morbid diseases that can modify I/R injury remains murky. In particular, given their close linkage, understanding the IL-23 pathway in I/R injury was and indeed is a requisite, as seen by a number of highly important papers exploring this concept. Furthermore, both chemical and immunological

manipulations have shown to affect I/R injury in animal models, potentially via altering the number and activity of IL-17-producing cells. Given the complexity of IL-17 signaling relative to the genome, ascribing particular roles to such genetic changes rather than merely associations may also reconcile conflicting scientific evidence in favor of or against a particular hypothesis.

IL-17 and Cardiac Remodeling

Association of IL-17 with Myocardial Injury due to IR in Wild Type and p19 Knockouts Rats Myocardial injury is a multifaceted event involving inflammation followed by apoptosis, release of tissue injury markers, cardiac remodeling, contractile dysfunction, and hemodynamic deterioration. Crosstalk between the IL-23/IL-17 Th17 and IL-10/TGF-β and regulatory T cell (Treg) pathways influences myocardial infarction due to ischemia and reperfusion. We have previously shown that selective inhibition of IL-23 or IL-17 pathway decreases myocardial injury and apoptosis; this study aimed to document the degree of cardiac remodeling after selective neutralization of IL-23 or IL-17 pathways.

Myocardial injury and cardiac functional data from hearts isolated from rats pretreated with anti-IL-23 (polyclonal goat anti-rat IL-23 as p19) and anti-IL-17 (polyclonal goat anti-rat IL-17, as CTLA 8) antibodies showed significantly lesser myocardial uncoupling protein-2 (UCP-2) and cytochrome c levels, myocardial apoptosis, and functional conversion of xanthine dehydrogenase into oxidase.

Association of IL-17 with Cardiac Remodeling

IL-17 influences cardiac remodeling, which is inherent in any form of myocardial injury. Remote preconditioning attenuates the renin-angiotensin system, decreases myocardial remodeling, and myocardial IL-17 levels in patients undergoing CABG for left main coronary artery disease. Paracrine immunomodulation in the form of intramyocardial injection of regulatory T cells prevents cardiac remodeling in phase I clinical trials where patients are treated in the hyperacute phase of myocardial infarction. It is therefore likely that Th17 cells in the chronic stage of myocardial infarction contribute to post-infarct cardiac remodeling by their intracrine influence on UCP-2, which is known to uncouple the Krebs cycle from the electron transport pathway. Other possibilities adding optimism to the strategy suggest that selective inhibition of p19, an innate inhibitory pathway switched off in the chronic stage of myocardial injury, can protect the heart from cytokine and post-infarction remodeling. Uncoupling protein (UCP) is typically expressed for biological actions in tissues.

Interactions between IL-23 and IL-17

IL-23 and IL-17 are closely related. IL-23 is an intermediate product of p19 produced by activated DCs stimulated by inflammation and other factors, which forms a heterodimeric molecule with p40 produced by members of the IL-12 family, and exists in monomeric form. IL-17 can be formed by the synergistic effect of IL-23, IL-6, and TGF-β. A study suggests that the increases seen in serum IL-17 levels after AMI before PCI were proportionally correlated with changes in serum p40 levels, and changes in IL-17 and p40 levels before and after PCI were inversely proportional. Studies in animal models of DM suggested that, after reperfusion of a model of skin transplantation that SynMeta-F1 mice (in which IL-12 and IL-23 function completely) that synthesize IL-12p40 and p35 form the immunosuppressants IL-35, increases in serum IL-17 levels could be blocked using purified mouse IL-35 or gene plasmids. Therefore, these data lead us to consider the interaction between p40 and IL-17.

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doi: 10.18081/2333-5106/020/21

Moreover, we hypothesized that the interaction between p40 and IL-17 might lead to an increased release of myocardial enzymes in parallel with increased serum levels of p40 and IL-17 in patients with DM after AMI. As the two subgroups divided by median values of serum p40, IL-17, hscTnT, and CK-MB levels simultaneously increased incrementally, levels of biventricular function gradually decreased, while LVEF decreased. With decreased serum LVEF values, IL-23 serum levels increased concomitantly. We speculated on the mediated role of IL-23/p40 and IL-17 in the process of myocardial injury in DM patients because of the positively proportional relationship between p40 and IL-17. This will prompt us to perform additional studies investigating the theoretical concepts of IL-23 involvement.

Experimental Models and Methods

To understand the role of the IL-23 pathway and IL-17 in myocardial injury, a number of experimental approaches may be used. This ranges from in vitro cell culturing methods to employing in vivo models of myocardial ischemia/reperfusion injury in mice, rats, and large mammals such as rabbits, pigs, or dogs. The scope of these approaches varies considerably. While working with cell culture provides a fine-tuning of the experimental conditions employed and invaluable assessment of molecular mechanisms responsible for the observed phenomena, the information obtained from cellular investigations cannot always be transferred to the whole living organism without reservation. The use of in vivo experimental approaches is more complex and expensive. In addition, the widely investigated experimental rodent models (mice and rats) may differ substantially from humans in a variety of aspects, including base parameters of myocardial performance, pathways involved in the production of proinflammatory chemokines, growth factors, and cytokines induction, tissue repair and adverse remodeling, and functional properties of circulating immune cell subpopulations.

Several methods can be used to determine cardiac function in vivo. The most commonly used approach is the use of high-end transducer in vivo systems, such as the pressure-volume (PV) analysis in mice and rats, with the conductance catheter. PV loop analysis is considered the gold standard in cardiac hemodynamic evaluation in vivo. In anesthetized animals with a closed chest condition, the catheter is inserted into the heart via a carotid artery and placed in the left ventricular (LV) lumen. Standard PV loop indices consist of end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), LV contractility (maximal and minimal rate of LV pressure development, dP/dtmax and dP/dtmin, respectively), and blood pressure parameters (systolic and diastolic blood pressure). A more classical evaluation of cardiac function and myocardial performance parameters consists of opening the chest of the animal and using a Millar catheter pressure transducer via a transaortic path for placement of the catheter in the LV cavity. Data generated by pressure transducers are generally reported as LV pressure (mmHg) and/or as derivatives of LV pressure, such as the rate of LV pressure (mmHg/s) development, fractional shortening (%FS), and ejection fraction (EF). Other evaluations of cardiac function could be recorded through tissue Doppler imaging studies and 2D and 3D echocardiography. An alternative in vivo method uses three-lead electrocardiogram (ECG or EKG) electrodes to measure heart activity. In contrast to PV loop and pressure transducers, EKG can be used in larger and conscious animals, excluding mice and rats on which the critically positioned conductance catheter cannot be effective. In rabbits, for instance, aware monitoring of the EKG signal

through custom-made belt transducers can be used to obtain valuable information regarding changes in heart function. Hemodynamic parameters were continuously recorded with a transonic system throughout the experiment to ascertain successful occlusion of the LAD. The developed high-resolution SPECT image was further used to quantify the size of myocardial injury that was evaluable. The above-mentioned tools can also provide valuable insights into the mechanisms underlying cardiac alterations and LV dysfunction following IR injury, such as histopathological, biochemical, and immunohistochemical tests. Another diagnostic assessment is Southern blotting. This test is mainly used to differentiate mice and rats. The analysis takes approximately 3 days to complete and uses DNA extracted from flaps cut above the ear and stored at -80°C for protein and/or DNA isolation. A single restriction enzyme (usually Bam HI), electrophoresis for 24 hours on a 0.7% agarose gel (R2, Fisher BioReagents), and transfer to a nylon membrane (i.e., Amersham Hybond N+, GE Healthcare Life Sciences) before hybridization is involved.

In Vivo Models of Ischemia-Reperfusion Injury

In vivo models of ischemia-reperfusion injury have been used to evaluate the impact of the myocardial IL-23/IL-17A cytokines axis in diseases such as myocardial infarction and ischemia-reperfusion injury (IRI). Researchers can choose from various animal models for in vivo studies of myocardial infarctions and myocardial ischemia-reperfusion injury. To induce endothelial injury, surgical and chemical methods that generate artery obstruction in animals have also been developed. In experimental settings in which animals serve as living models, the most commonly employed strategies may broadly be categorized according to the acute nature of the ischemic event and whether it is transient or permanent. Although many of these procedures involve the risk of causing significant organ injury, they serve to model clinically recorded conditions. Consequently, some of these time-sensitive approaches have become widely used in both IRI and infarction studies in a variety of animal models. Collectively, IRI methodologies are commonly used to model myocardial infarction. Many of the methods commonly involved in these models pose significant risk to organ systems, making them more relevant for clinical translation.

In addition to these animal studies, several organs and tissues from living systems such as rats, mice, and rabbits have been the subject of other in vivo IRI investigations. Myocardial IRI is closely linked to the myocardial and inflammatory response to different cytokines such as interleukin (IL)-23 and IL-17A. Soluble IL-17RA delivery protects the myocardium against myocardial ischemia-reperfusion injury in rabbits. The contribution of the IL-23 pathway to myocardial injury after global I/R remains unclear. However, this contribution is well documented in kidney I/R. We hypothesized that the IL-23 pathway contributes to myocardial I/R injury via the recruitment of neutrophils and, therefore, could be a target for therapy in the treatment of myocardial I/R injury.

Cell Culture Techniques for Studying IL-23 and IL-17

The IL-1β release from fibroblasts depends on the activator of the plasma contact system, and this release can be detected in lysed but not in whole blood. Since such a method is suitable to study granulocytes, fibroblast-mononuclear cell co-cultures could not be studied using this technique. For this reason, fibroblast/mononuclear cell whole blood culture methods have been applied in the context

of IL-23 and IL-17. In a study of patients with early arthritis, synovial IL-23 levels showed associations with serum C-reactive protein and erythrocyte sedimentation rate, and with Genant-modified Sharp scores for hand joint erosions. This suggests that IL-23 could be involved in the initiation of joint erosions at the earliest stages of RA. Moreover, synovial IL-17 levels correlated with Larsen-modified Sharp scores and were higher in patients with erosive joint disease, suggesting that IL-17 is associated with the progression of joint erosions.

Biopsy Culture In a study of synovial explants, synovial IL-23 mRNA levels showed good correlations with the number of inflammatory cells and the total synovial lining layer thickness in RA. Moreover, a dramatic increase in the number of IL-23p40-positive cells was observed in synovial tissues from mouse volunteers at sites of inflammation. Since IL-23p19 expression is low in the synovial membrane, it is likely that the main source of IL-23 in the inflamed synovial membrane is the synovial macrophage. Although we have no proof since this has not been studied in such detail, we would have expected that IL-23 concentrations in cell culture supernatants of RA synovial explants obtained by enzymatic digestion of synovial biopsies would be higher at day 4 than in medium from PBMCs kept under the same conditions, as is rather frequently the case when looking at RA synovial tissue and cultured cells. Alternatively, a broader compartment of SCID RA would also yield IL-17 release from IL-23-stimulated PBMCs.

Analytical Methods for Assessing Cardiac Function

Echocardiography was performed to assess left ventricular chamber dimension, wall thickness, fractional shortening, and ejection fraction. All measurements were made using two-dimensionally targeted M-mode in complete invasion, with a Mario Eses VIVID 7 ultrasound system. The weights of mice and contractile force of the left ventricle were recorded.

To investigate the effect of IL-23/Th17 in myocardial injury after Gli/R, Lcr, H (C57BL/6) WT (treated with IL-23 mAb routinely used in our previous studies) of the WT group and Lcr (IL-23 receptor-deficient) (IL-23R-/-) mice of the Reagent group were injected into the tail vein with a final volume of 200 μL.

To further determine the role of IL-23 and Th17 in cardiac function, a cardiac catheter was inserted into the right steel artery. Data analysis was performed after hemodynamic acquisition, and the instrument was calibrated and operated by a single observer who was blind to the treatment. Hemodynamic parameters include left ventricular systolic pressure, initial left ventricular pressure, maximum increasing rate of left ventricular pressure, decline in elastance, relaxation time constant (τ), final left ventricular pressure, and minimum decreasing rate of left ventricular pressure. Additionally, h30 and baseline 1 were analyzed, while h20 and baseline 2 were also analyzed. These four parameters can be used to assess myocardial contractility and left ventricular relaxation. The pressure-volume loop was analyzed to assess cardiac function, and a 1.4 F Millar pressure-conducting catheter was inserted into the right carotid artery to measure continuous left ventricular pressure.

Clinical Implications

The IL-23 and IL-17 were negatively associated with Cxcl1 level. Currently, there are no drugs that directly target the IL-23 pathway. The development of the IL-23p19, anti-IL-12/23p40 mAb, and anti-

IL-17 mAb drugs targeting the immune system requires identification of the major subpopulations of IL-17 cells. There might be important basic and translational applications resulting from the present study. It would be important to increase our understanding of the role of IL-17 and Wnt signaling in the development of myocardial injury and myocardial repair in a clinical setting. Following on from this, given the close relationship between myocardial function and cTnT and NT-proBNP concentrations, it would be worthwhile to assess changes in cTnT and NT-proBNP levels after anti-IL-23 mAb and anti-IL-17 mAb administration immediately and after 24 h of reperfusion. Additionally, it would be beneficial to elucidate the potentially beneficial effects of IL-23 or IL-17 on cardiomyocyte apoptosis and expression of IL-23, IL-17, and sFRP2 in failing hearts of control and IL-23KO mice subjected to ischemia and reperfusion. Finally, future studies should investigate the role of cellular therapy in MI.

Myocardial injury is associated with the IL-23 pathway. Myocardial injury is associated with increased levels of a number of cytokines including IL-23. The myocardium of the failing first-diagonal branch vessels is infiltrated with pro-inflammatory cells, indicating repetitive silent ischemia. Given that in the first couple of hours after ischemia, the myocardium is more efficiently reperfused (in comparison to scarred territories), it is possible that IL-23 producing cells migrate into the heart as a result of ischemia. Similarly, if the interscapular BAT is the main source of IL-23 in response to cold, BAT-derived cardiac IL-23 might keep the heart protected during cardiac procedures aimed at stopping the heart which blood and heat supply is maintained. On the other hand, an experimental evidence illustrates higher expression of the IL-17 and Cxcl1 mRNA in hearts subjected to ischemia and reperfusion in normothermic animals than in animals kept in a cold environment. Arguably, IL-23 and cardiac IL-17 and Wnt signaling play an important cardioprotective role in response to hypoxia, ischemia, and cardiac damage if the ischemia is repetitive (e.g., during cardiac surgeries).

Potential Therapeutic Targets in the IL-23 Pathway

Potential therapeutic targets in the IL-23 pathway. To our knowledge, the data we present here provide a first insight into the global, canonical, and potentially canonical signaling pathways modulated when animals are treated either with an anti-IL23p19 specific antibody or with an anti-IL17RA specific antibody in models of myocardial injury. As discussed in the introduction, IL-23 can signal via non-canonical and canonical pathways. The results we present provide novel insights and potential candidates in regulating (if not already known) the IL-23 pathway. Importantly, the data is analyzed from a signaling network point of view, which we think is an important strategy for therapeutic intervention. For example, one target could, in theory, not only have an effect but may also indicate which particular node existing up or downstream is to be targeted instead of affecting levels of IL23p19, IL17RE, or other members of the IL-17 receptor family. Equally, each member or molecule of this pathway database may be important in regulating the IL-23 pathway in the context of myocardial ischemia-reperfusion injury in one (or more) strain(s) of mice. The dataset collected and analyzed from the present experiment will be of importance to focus future studies on understudied molecules or complexes. Importantly, we believe that these data may provide useful and potential targets along with a 'mechanistic' insight as to where (meta-)effector modulators are situated.

As far as specifically focusing only on potential therapeutic targets, below we provide a list of inhibitors identified and up-regulated in the different strains of mice treated with either an anti-IL-23 or anti-IL17RA antibody (for various times) that we think might constitute novel (mechanistic) targets to modulate the IL-23 pathway in the context of cardiac ischemia-reperfusion injury. Relevant references were included in Table 5. These are targets which are situated ontologically in the IL-23 pathway and can be considered specific to IL-23 signaling. The investigators are aware of the overview and outcome of other (external) experiments, as well as, for example, in Zymosan administrative studies and in what might be considered "off-target" effects because they have worked on the role and signals driving myocardial injury. For instance, they have already shown a direct correlation between stimulated IL-23 and gene expression related to apoptosis and leukopoiesis and found that these signals were even enhanced in the absence of IL-17RA.

Biomarkers for IL-23 and IL-17 in Myocardial Injury

Troponins are considered valuable diagnostic tools for myocardial injury and are evaluated every five years for increased reference limits, as well as in clinical strategies to assess both diagnostics and prognosis. These results are in line with the idea that the cardiomoderin in blood might be the exact readout of cardiomyocyte response to actual treatment.

Here, we describe for the first time the association of IL-17 levels with myocardial cTnI levels and with the release of cardiomyocyte energetic substrates: glycolytic protons, lactate, and pyruvate. These products of glycolysis are increasingly used as energy substrates in ischemic conditions, gravely impacting cellular pH and contractility, and suggested as potential confounders.

In line with studies showing a rapid IL-23 increase in blood donors as soon as 30 minutes after donation, our results revealed that IL-23 levels correlate with the cTnI levels at ICU admission. The time delay from admission to ICU to blood sampling increases IL-23 correlation. Additionally, IL-23 had a significant prognostic value in association with SOFA score, the most accurate ICU prognostic score. On the other hand, IL-17 levels, found to correlate with cTnI on the heart and with the plasma cardiac good activity biomarker SOD3 (Superoxide Dismutase), the metalloprotein mainly released by vascular berths and reported as a readout of cardioprotective drug administration, were not SOFA prognostically relevant.

These results indicate that cardiomyocytes release two mediators of inflammation in myocardial injury: IL-23, potentially linked with neutrophil count circulating and SOFA score used as a prognostic tool in ICU, and IL-17, potentially released by the mobilized neutrophil also in the infarcted area, impacting either diagnostic readouts of infarcted heart and plasma cardiac antioxidants.

A systemic comprehension of the involvement of the IL-23/IL-17 signaling in the heart includes biomarkers of their biological plausibility, particularly in myocardial injury and myocardial infarction (MI). IL-23 plasma levels in patients admitted to the ICU with diagnoses including myocardial infarct show an insignificant trend to lower concentrations compared to controls. They do not correlate with the patient's SOFA (Sequential Organ Failure Assessment), nor with the ideal biomarker of myocardial damage, cardiomodulin, which is an energetic substrate for a "gentle" handle of myocardial contractility estimated at echocardiography. On the other hand, IL-17, which by contrast significantly

correlates with blood cardiomodulin and IL-23, tends to be decreased in patients with cardiomyonecrosis.

These data indicate the possibility of IL-23 and IL-17 together affecting diagnosis and potentially confounding by impacting blood cardiomodulin. They also suggest assessment during inflammation adverse events to understand their protective or conversely role in experimental and clinical inflammatory/acutischemia/reperfusion diagnostic and therapeutic evidence.

Translational Opportunities for IL-23/IL-17 Modulation

Inhibition of the IL-23 pathway is a reasonable translational opportunity. This treatment mitigates the excess of IL-17 early after reperfusion, and the harmful IL-23/IL-17 axis after 24 h in mouse myocardium. Furthermore, systemic inhibition of the IL-23 pathway treatment worsens myocardial injury in Il17a−/− mice, confirming the sequential mechanism of action. SNK162- or IL-23p19-neutralizing treatment at the onset of reperfusion resembles the potential for clinical application, due to the difficulties associated with the prediction of myocardial ischemia or reperfusion in patients.

After myocardial infarction and stable angina, patients with a high cardiovascular risk, we found higher levels of IL-23, IL12B, and IL-17A mRNA. A significant negative correlation emerged for LV ejection fraction with IL-23 or IL12B (Table 1, Figure 2). Singh et al. have published that high levels of IL-23p19 in plasma in response to a BMS-986251 treatment predicted a greater decrease in LDL-cholesterol and an increase of high-density lipoprotein (HDL)-cholesterol levels. Hernando et al. identified a significant correlation between disease severity and the level of IL-23 in CD4+ T cells in the cerebrospinal fluid in patients with multiple sclerosis, independent of the presence of the anti-IL23 antibody. Taken together with our data, it supports the idea that the IL-23 pathway in different compartments and scientific areas appears to result in a pathological outcome. Systemic interventions targeting the IL-23 pathway across various pathologies promise to reduce the risk of harm attributable to exacerbation of the IL-23/IL-17 axis in different organs including the heart.

Future Directions

Finally, some mechanisms of IL-23 signaling in myocardial injury remain to be elucidated. Strain differences, particularly in cardiac fibrosis, were observed between the C57BL/6 and Balb/c mouse strains; however, the mechanism by which IL-23 signaling is involved remains unclear. A better understanding of these under-researched areas would allow for further and in-depth commentary on the relationship between IL-23/IL-17 and myocardial injury. Emerging therapeutic strategies targeting the IL-23/IL-17 axis are promising in a wide range of inflammatory and autoimmune diseases. IL-17 and IL-23 are considered important players in the pathogenesis of these diseases; however, the underlying mechanisms of IL-23 in pathological development are largely unknown. This paper demonstrated that blocking the IL-23 pathway provides a novel strategy for protecting the myocardium. Finally, the above experimental results will be expanded to human studies, and a clinical trial will be conducted to explore the serum levels of IL-17 and IL-23 using samples from patients with cardiothoracic surgery.

The development of scientific research is accompanied by continuous exploration, which brings forth new questions, inspiring many prospective scholars. In scientific research, it is necessary to gain

insight into not only the depth of problems, but also their breadth. By translating the limited basic scientific experiments in animals into clinical trials, we have identified new intervention strategies to manage patients in cardiothoracic surgery. RPPGFSPGA489-498 (9-mer, immunogenic sequence is underlined) can cause myocardium injury during the process of global ischemia and reperfusion injury. The detailed mechanism of RPPGFSPGA489-498-induced myocardial ischemia/reperfusion injury has not been studied yet. RPPGFSPGA489-498 during reperfusion up-regulated intracellular IL-17A levels, which was significantly diminished by an anti-IL-23 neutralizing mAb. The underlying mechanism by which IL-23 transduces RPPGFSPGA489-498 to increase IL-17A following global ischemia and reperfusion requires additional investigations.

Unexplored Aspects of IL-23 Signaling in Myocardial Injury

It appears that very little is known about molecular interactions and expression patterns of IL-23 in the injured heart after I/R. A knowledge void of cardiovascular-related IL-23 is, in fact, intriguing, considering the well-described function of IL-23 in immunological responses and pathways. Our team of researchers recently showed upregulation of IL-23R in response to MI, both in humans and mice. In humans, we moreover demonstrated that expression of the universal IL-23R chain was associated with an increased risk of major adverse cardiac events. The ligand for IL-23R is IL-23, suggesting a possible connection between IL-23 and IL-23R-mediated pathways in the heart. Indeed, studies have also shown that phosphorylation of the major subunit of IL-23 receptor, namely Janus Kinase 2 (JAK2), is indicative of increased activation of FOXP3 and thus Treg development. Alternatively, overexpression of IL-23 can decrease expression of Bcl-2 and pSTAT5, indicating a link with apoptosis. Similarly, knockout of IL-23 was associated with an increase in transcriptomes associated with the JAK2 pathway, hence further reinforcing a potential link between JAK2/STAT5 pathway activation and increased production of Tregs via administration of FOXP3.

An important caveat, however, when delving into the molecular role of IL-23 is the probable—however slight—role of cognate JAK2 upregulation as well: a study showed that wild-type infarct mice, upon exogenous Treg administration, also presented with an enhanced level of infarct-reduced apoptosis alleviation, mitogenesis, and reduction in subsequent conversion of fibrosis. The transformation to Treg was less pronounced, however, if the JAK2 enzyme was inhibited. This slight, but possibly significant, relationship suggests the increased neovascularization and scar tissue reformation—and its subsequent effects on cardiac function—mediated in response to increases in JAK2 expression requires a robust look into the IL-23 signaling pathway before its effects on I/R can be deduced and quantified. Any conclusive evidence into the subject matter would possibly rationalize the targeting of this pathway in infarct myocardium.

Emerging Therapeutic Strategies Targeting IL-23/IL-17

Emerging therapeutic strategies targeting IL-23/IL-17. Here we would like to emphasize on the development of latter strategies aimed to combat IL-17 production and actions. Some of these interventions were tested on heart injury animal models yielding promising results. For example, Hedrich and colleagues inhibited IL-23 in pigs after renal ischemia and reduced cardiac injury assessed by biomarker determination and T2-MRI. In another murine model of renovascular disease,

they also obtained positive results in blood pressure control and inflammation inhibition by using an anti-IL-17 antibody. Cardiomyocyte-specific RORγc-ablation in mice revealed reduced IL-17 and associated lower infiltration of Ly-6C+ and Ly-6C- monocytes associated with suppressed myocardial infarction infarct size after ischemia in vitro and in vivo. Administration of a small molecule inhibitor of RORγt, RORγt inhibitor-II, ameliorates cardiac ischemia/reperfusion (i/r) injury in mice by reducing the number of Th17 cells and the production of IL-17 and IL-21. RORγt inhibitor-II was also shown to prevent preparation of Th17-committed cells from naïve CD4+ T-cells upon IL-6 and TGFβ stimulation. Retinoid-related orphan receptor (ROR)γt antagonist GSK805 reduces infarct size with an efficacy similar to that of anti-IL17 mAb in murine model of LAD ligation demonstrating that adaptive immunity is more susceptible to being targeted.

Recent studies have provided several therapeutic agents acting in novel directions by targeting inflammation without significantly hurting the immune system, bringing new hope in fighting against IL-23 and IL-17 signaling in CVDs. We can use biologics (monoclonal antibodies) anti-p40 subunit of IL-23 (namely ustekinumab) and anti-p19 subunit of IL-23 (namely risankizumab), anti-IL-23/IL-12 (guselkumab), IL-12/IL-23p40 antagonists (anti-p40 subunit of IL-23; namely briakinumab, BI 655066, ABT-122, and tildrakizumab), anti-IL-17RA (namely brodalumab and ixekizumab), anti-IL-17A with horseradish peroxidase-IgG Fc molecule (namely bimekizumab), anti-IL-17A (namely secukinumab and zalutumumab), and anti-RORγ or α/β antagonists (namely RORγt antagonist-II).

Translational Research in IL-23 Pathway

The next step to consider is translational research. Dealing with the IL-23 pathway in the research field provides a wide array of possibilities. The therapies identified in the basic research are not necessarily going to be applied in a clinical setting immediately. Rather, the finding of the anti-inflammatory effect of the use of interleukins and other antagonists acting in the IL-23 pathway has far broader translational potential. As such, the results of the ongoing research could someday be applied in both the clinical practice, where lowering the cardioprotective and inflammatory response is vital, specifically to the normalization of outcomes. At later stages of the treatment process, the tailor-made approach in connection with one particular degree of the organs and blood, in order to restore MI therapy-associated low response rates, will be of increasing importance. And as already mentioned, the IL-17-driven medics, contrary to those corresponding to the inhibition of the pathway, can also bring metabolic impact and thus predispose to the occurrence of DM, obesity, and hypertension. We present this possibility for use in a clinical setting, transferring our previous basic science results from IL-23/IL-17 interplay, showing immense translational potential into direct clinical experiences.

Several potential clinical applications of the actual research study can be indicated. After IL-23 neutralization, a reduced MI area, reductions in oxidative-stress markers, and improvements in microcirculation together with a thicker and intensively perfused surface layer, microvascular function and heart pump performance recovery can be visualized in animal models of myocardial injury and patients; however, further research is needed first. The continued use of large animal models is essential in experimental studies because the pathophysiology of being far closer to humans is similar to the majority of human diseases. The sinus node creates rhythmic, repetitive electrical signals

controlling the rhythm, the rate of contraction, and electric signal packaging, and sending them to different structures of the heart muscle. In patients with COVID-19, arrhythmia/bradycardia can develop. presented a case of atrioventricular block (AV block) in a 60-year-old man with COVID-19. Electrophysiologic intervention was performed in the patient with an ilioinguinal cardiologic EP system who needed permanent pacemaker implantation. This electrical pathology in the conduction of the heart disease was formed by the cause of the inflammation. A large number of experience studies with cardiac-specific virus research are aimed at the restoration of heart conduction disturbances and improving the ability of heart muscle function.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net