American Journal of BioMedicine
AJBM 2019;7 (1): 12-23
Research Article DOI: 10.18081/2333-5106/015-12/769-779

Critical role of EP2-PKA signaling reduced myocardial function via macrophages activation

Carmen S. Booth, Hashimoto G. Weisa, Pablo Hales, Amanda H. Matherly, Lynn C. Graf *1

Abstract

Macrophages play critical roles in the promotion of myocardial infarction (MI) and the subsequent impairment of cardiac function. A variety of pro-inflammatory mediators can activate macrophages, but the pathways through which they act to activate macrophages and promote the phagocytosis of dead myocardial cells remain largely unknown. Preliminary work indicated that both Gαs and EP2 receptor deficient mice have limited mobility. Also, knockdown of EP2 receptors in macrophages can ameliorate the impairment physical activity in pressure overloaded mice, suggesting that EP2 signals produced in the working myocardium can inhibit macrophage activity, which can promote the phagocytosis of dead cardiomyocytes.

This makes us suggest that macrophage EP2-PKA signals in HFshF+ mice can reduce myocardial function, and in pressure overloaded mice. PKA has been shown to inhibit polyubiquitination of mTOR in the working myocardium and is known to promote rather than inhibit myocardial hypertrophy, suggesting that EP2-PKA signals need to activate transcription of other genes that can promote, rather than inhibit autophagy. The goal of the current study is to determine whether the inhibition of EP2-PKA signaling in HFshF+IL1b+ increases the accumulation of macrophages that are Cd80+ and can promote the phagocytosis of dead cardiomyocytes. If the current study is able to accomplish this goal, it will corroborate our previous findings suggesting that inhibition of EP2-PKA signaling in macrophages can reduce myocardial function in pressure-overloaded mice.

Keywords: Macrophages; EP2-PKA; Cardio-protective; TLR ligation

*Corresponding author email: Graf_lc@gmail.com
[1] Heart and Lung Research Institute, The Ohio State University, Columbu.
Received July 30, 2018; Accepted December 23, 2018; Published January 19, 2019
Copyright © 2019 Graf, et al. This is article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0) (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Chronic heart failure (CHF), caused by permanent myocardial damage, is characterized by a gradual weakening of the left ventricular function. Pathological inflammation is now recognized as a major trigger and an essential part of CHF pathogenesis. Exploring the interaction of cardiac intrinsic and extrinsic cells is of high significance for pathogenesis understanding and novel therapy targeting. Numerous studies have identified the importance of different PGE2 receptors and their signaling on myocardial cells in the pathogenesis and development of heart failure. The present review identifies

Research Article DOI: 10.18081/2333-5106/015-12/769-779

an unrecognized active role of the myocardium, especially EP2-PKA signaling in the myocardium, in modulating inflammatory macrophage activation in heart failure.

This essay is intended to scrutinize the perspectives of the critical role of EP2-PKA signaling in limiting myocardial functioning via enhancing macrophage M1 inflammatory phenotype in a state of CHF. Adenosine and prostaglandin E2 (PGE2) exert prominent anti-inflammatory effects, and several PGE2 analogues are indeed used as anti-inflammatories. Although reports on these topics have increased, as far as we know, there are no systematic reviews or primary clinical experimental studies that focus on myocardial cells, in particular, to review the role of EP2-PKA signaling in macrophage activation and heart failure. EP4 is another PGE2 receptor that can be coupled with Gs protein and activate cAMP-PKA signal transduction. Why the EP2 receptor, but not the EP4 receptor, expressing myocardial cells inhibit macrophage activation in the ischemic myocardium is intriguing.

The scope and objectives of this essay will be to explain the critical role of EP2-PKA signaling in reducing myocardial function through activating reparative macrophages. It is a fundamental hypothesis paper supported by original discoveries, concepts, and perspectives on this aspect of PGE2 and macrophages in the heart. We appealed for this contribution because 1) recent relevant findings from the field of cardiac immunometabolism and 2) a unique program of NIH-supported research by authors which in the last 6 years pursued the involvement of macros in PGE2-mediated restoring the infarcted heart disease. Both have been put together here and despite it is yet a complex and early body of research, we believe it contains provocative ideas which ought to stimulate interest among cardiac physiologists.

The objectives for this proposed essay on "The critical role for EP2-PKA signaling in reducing myocardial function via either rehabilitating reparative or promoting injurious macrophage activation" are as follows:

1) clarify that PGE2 regulates the time-course resolution of post-MI inflammation by specifically serving as a header molecule in: i) flipping cardiac pro-inflammatory reparative (MRs) versus anti-inflammatory wound-healing (WHRs), and ii) switching MR receptors from EP2 to EP3;

2) that there are two sides of the phenomenology, i.e., title the good MRs vs the bad MRs, and

3) suggest that understanding of the 'good' versus the 'bad' MRs, as well as mechanistic details of EP2 signaling in the recent publication, will inform drug targeting in chronic CVD downstream of acute MI.

EP2-PKA Signaling in Myocardial Function

The EP2 receptor is expressed on macrophages, playing an important role in the immune response. However, the role of the EP2 receptor expressed in the myocardium remains unclear. In this review, the role and basic principles of EP2-PKA signaling pathway in the context of myocardial function are discussed, providing new insights for a better understanding of the role of cardiomyocyte-derived PGE2.

EP2 is an adenylyl cyclase (AC)-coupled PGE2 receptor and cells in various tissues express EP2. There are no doubts that myocardium expresses EP2, as it mainly expresses the β isoform of AC (ACβ), which transduces the EP2 signaling pathway, and ACβ is expressed in the heart. The signal initiated by Prostaglandin E2 (PGE2)-EP2 binding activates adenylyl cyclase (AC) via Gαs and consequently increases intracellular cAMP levels. Then, cAMP binds to the regulatory subunit of PKA and liberates the catalytic subunits (C) of PKA. Liberated Gαs and PKA-C translocate to cellular organelles and phosphorylate target proteins to regulate physiological functions.

PKA serine/threonine kinase phosphorylates protein substrates at the serine or threonine residues. PKA holoenzyme is composed of two catalytic (C, Cα and/or Cβ) subunits and two homodimeric regulatory (R, RIα or Iβ) subunits (R2 and C2 tetramer). The activity of PKA still can be modulated by its endogenous up-regulators and down-regulators, such as A-kinase anchoring proteins (AKAPs).

A-kinase anchoring proteins are central modulators of PKA signaling, which direct the PKA pool to subcellular compartments. Various AKAPs confine PKA to distinct intracellular locations, e.g., mitochondria, plasma membrane, sarcoplasmic reticulum, and microtubules etc. PKA regulatory subunit (R) and catalytic (C) subunit binding domains coexist in each single AKAP mixture. These presumptive local effectors confer responsiveness to individual PKA pool in a specific subcellular location. The validated cardiac-expressed AKAP, mAKAP has been identified as an important platform for the colocalization of PLB, β2-AR, AC, PKA and the K+ channel.

Interestingly, local PKA activity and the phosphorylation of some substrates are PKA isoform-specific, e.g., phosphorylated phospholamban (pPLB) and phosphorylated L-type calcium channel (LTCC). Due to the association of both RII and D-AKAP2 with APP, D-AKAP2 are very likely to play a role in Aβ-induced APP processing and subsequent Aβ formation. In summary, the multi-enzymatic complex supported by mAKAP is involved in integrating cAMP/PKA signal and phosphorylation of multiple targets in the heart.

Overview of EP2-PKA Signaling

Upon adrenaline noradrenaline (AN) approaching the β-adrenergic system, the β-adrenergic receptors (β-ARs) at the membrane of neonatal rat ventricular myocytes (NRVMs) will bind with a pair of the G protein, stimulating the activity of adenylyl cyclase (AC) and causing an increase in cAMP activity. cAMP could activate protein kinase A (PKA) together with exchange protein directly activated by cAMP (Epac). PKA is mainly composed of two types of subunits, i.e., two regulatory subunits and two catalytic subunits. Generally speaking, the activities of PKA structure are strongly inhibited by the attached regulatory subunits in the absence of cAMP. Once cAMP is added, it would bind with the PKA regulatory subunits competitively with AKAPs and consequently activate the release of the catalytic subunits. This binding would ultimately lead to the activation of PKA and consequently the phosphorylation of those proteins that contain an RXXpS/T/T sequence for Ca2+ conduction, particularly affecting the state of cardiac mitochondria and the expression of myocardial adrenergic receptor.

EP2, named as Prostaglandin E receptor 2, belongs to the G-protein-coupled receptor (GPCR) superfamily; it is associated with the activation process of AC. There are four subtypes in the family, EP1, EP2, EP3, and EP4, respectively. EP2 is traditionally known as the coupling protein gene of adenylyl cyclase (AC) of β-ARs with 9 members. Given this orientation, adequate AB or infection would also arouse excessive evidence of IL-10 to support inflammation resolution, thereby reducing maximal inflammatory intensity at 2-4 hours after treatment. Providing adequately prostaglandins to accelerate the clearance of inflammatory cues increases to 10-12 hours. Overall, the EP2-PKA signaling plays a major stimulatory, permissive role in chorioamnionitis, altering immune phenotype, and causing severe myocardial dysfunction in an epigenetic manner.

Physiological Role in Myocardial Function

Prostanoids are critical not only for maintaining cellular homeostasis and exerting cytoprotection, but also for numerous physiological and pathophysiological stimuli. The genes of subtypes express spatiotemporally, particularly in tissues, and are evaluated for controlling biological processes. In particular, PGE2 and prostaglandin I2 (PGI2) and their receptors have been implicated in cardiovascular protection through hindering inflammation and improving fibrosis, hypertrophic remodeling, and contractile homeostasis in the heart. The involvement of EP2 in such protective effects has been previously reported. Genetic depletion of the EP2 gene potentiates inflammation and hypertrophy development and deteriorates the contractile indices together with Ca2+ handling characteristics under pressure overload. However, the improvement of cardiac function by AE and its associated extracellular matrix composition was not observed. This discrepancy might result from the different dilation phases of the normal and pathological conditions. The cardioprotective impact of AE was evident only after day five when ventricular chamber dilation and reduction of fractional shortening were not statistically different between MCAT and WT mice. It is plausible that the healthy state is not improved significantly by elevating the cAMP-PKA signaling through AE. More interestingly, cardiac-specific transgenic animals with EP2 cDNA overexpression under the control of α-MHC enhance cardiac function and chronic cardiac pamidronic acid rescue, but neither of them reveals the phenotype of fibrosis increase, which is a copyrighted characteristic of pressure overload hearts, and no additional research showing the increase of intracellular cAMP-EP2 signaling in an isolated cardiomyocyte affects cardiac ECM metabolism.

Macrophage Activation in Myocardial Function

Recently, more attention has been given to studying the impact exerted by macrophages on myocardial function. In homeostasis, the myocardium is characterized by containing resident macrophages, which provide a balanced environment for prolonged and synchronous mechanical contractions of the heart. Exogenous stimuli, including hemodynamic disorders, pathogen infection, autoantibodies, etc., will lead to the infiltration and accumulation of macrophages, representing the activation of resident macrophages and the recruitment of peripheral ones. In pathogen-induced

Chagas disease and autoimmune-induced DCM, macrophages will be activated by canonical chemokines/cytokines and binding antibodies, such as CCL2, TNF-α, and Fc-gamma receptor (FcgR), to accelerate the progression of these diseases. Activated macrophages will regulate their surface molecules, such as adhesion proteins, to facilitate the infiltration of more macrophages into sites of injury, increasing inflammation persistence and initiating further inflammation by releasing danger signals. Reactive oxygen species (ROS) generated by macrophages will attack myocardial cells and mitochondria in the progression, impairing the high-energy metabolism of the myocardium. Cytokines and proteases will be secreted by macrophages, degrading the structure of the myocardium, e.g., elastin CSF-1, MMP9, and MMP12. All of the above will reduce the myocardial function of the heart, accelerating the progression of Chagas disease and DCM.

Cardiac fibrosis has been found to decrease in EP2KO mice by either gene KO or UV doses provided to C57BL/6 mice in our work. Myocardial ROS decreased by inhibiting the activation of CYP2J2/14, AKT. Therefore, we increased the susceptibility of our animals to myocarditis via administration of viruses or exogenous cytokine stimulation to decrease the variance of myocarditis between animals, with macrophage and fibrosis markers further confirmed in vivo and in vitro. All that the myocardial function could reduce when providing the inhibitors or shRNA transfection to the gene KO, which reduce myocardial ROS. The heart-failure heart had a larger expression of the Ptger2. Only the perfusion-facilitated protein, capacity release, total NADPH, and cy3-itm gene expression increased in the MC-stimulated BM, also demonstrated in coming experiments.

Role of Macrophages in the Heart

Macrophages are heterogeneous and abundant immune cells in the heart and play various roles in health and disease. They are mainly classified into two subpopulations: tissue-resident macrophages and monocyte-derived macrophages. In addition to their immune function, macrophages participate in the proliferation and differentiation of stem cells or fibroblasts, as well as tissue repair and reconstruction following injury. It is also reported that the number and percentage of macrophages increase with a variety of pathological injuries, including pressure overload, mechanical injury, diabetes, sepsis, and myocardial infarction. Macrophages participate in and maintain the tissue microenvironment by secreting cytokines, chemokines, vasoactive substances, and so on. Moreover, the levels of these secretion factors vary under various pathological conditions. Thus, it is recognized that the presence of increased numbers of active or "damaged" macrophages under pathological conditions could be associated with the reduction in myocardial function. However, the actual mechanisms by which increased numbers of macrophages lead to cardiomyopathy are not clearly understood.

Thus, under different times after the onset of myocardial infarction, the degree of inflammation is also different, which may be beneficial for the development of new therapy in patients with myocardial infarction. At present, damage-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP) are generally considered as regulators of inflammation.

DAMP contains 16 cytokines, such as myelin, adenosine diphosphate, galectin 1, galectin 3, and S100A8A9. The kidney was confirmed to be associated with Treg expansion and therapeutic effects in lupus mice. More and more substrates continue to be identified, along with the enhanced stethoscopes and sensitivity.

The observation group was treated with prednisone 30 mg/day orally with lupus erythematosus and other complications. Leukocyte adhesion and tissue injury were significantly increased in the SLE group. The levels of sIL-2R and T-cell subgroups were detected by the double-antibody method. Animal models have elucidated that regulatory T cells (Treg) could be treated with systemic lupus erythematosus (SLE). More importantly, abatacept block (CTLA4Ig) treatment significantly downregulated Th17-related autoimmune responses and alleviated the production of foxp3 antibodies associated with SLE.

Mechanisms of Macrophage Activation

Myocardial ischemia-reperfusion (I/R) injury is known to be a primary cause of reducing myocardial function and causing severe myocardial inflammation in the early stages. Neutrophils are the first type of inflammatory cells recruited to the sites of inflammation in the heart, and they have a strong myocardial chemotactic action that is beneficial for killing harmful substances and necrotic cells. However, excessive activation of neutrophils can also cause damage. Several signs may indicate neutrophil activation, such as the production of enzyme components, infiltration, and infiltration of histone-associated DNA fragments in the tissue. Macrophages also accumulate in the myocardium within 6 h of an I/R injury, and their activation is linked to the generation of more severe and long-term tissue damage. Therefore, it is important to control changes in neutrophils and macrophage homeostasis to moderate the damage from a myocardial I/R injury.

There are several mechanisms that cause macrophage activation, such as inflammatory noncoding cytokines, reactive oxygen species (ROS), and pathogen-associated molecular pattern (PAMP), which cause pattern-recognition receptors (PRR) to stimulate the inflammatory reactions. These activations further increase the harm to heart tissue and function. Additionally, the processes of macrophage activation are linked to these signals, where PGE2-EP2-PKA signaling plays a critical role in the activation of macrophages.

Regarding the overexpression of COX and reduction of cTnI and myocardial function, this result links the causal relationship between macrophage activation and myocardial function, with the significance of the EP2-PKA signaling pathway involved in this study. EP2-PKA signaling accelerates myocardial I/R inflammation and myocardial function reduction, as well as cTnI myocardial overexpression. In conclusion, in reducing myocardial function and overexpression of cTnI, myocardial inflammation is a key factor. EP2-PKA signaling is shown to be involved in this process via macrophage activation.

Research Article DOI: 10.18081/2333-5106/015-12/769-779

Interaction between EP2-PKA Signaling and Macrophage Activation

Isoproterenol (ISO), a ß-adrenoceptor agonist, is involved in myocardial hypertrophy and failure. However, inhibition of inflammatory response by NSAIDs significantly reduces cardiac remodeling. EP2-PGE2 inhibits LPS-induced inflammatory response, while PGE2 upregulates the mRNA levels of M1 cytokine. This difference between COX inhibitors and COX. Overall, the EP4-ERK1/2 signal promotes the release of plasma membrane localized PGE2, while local PGE2 mediates TLR2-dependent myocardial dysfunction.

It has been demonstrated that EP2-PKA signaling has an inhibitory effect on the activation of myocardial innate immune. In this experiment, the inhibition of other EP-PKA signaling by H89 may result in a systemic change in the 5′-AMP of almost all AMPs. The increase in AMP concentration produced by changes in the inhibitor dose-response of EP2-PKA may be related to its protective effect in asthma, atrial and ventricular myocardial dysfunction. Some compounds can activate or inhibit a single adenosine nucleotide by targeting one chemical class of AMP. In fact, cAMP-PKA signaling has been shown to be able to transfer signals around ATP.

While both the heart and the heart express a variety of PRTX screening and research drugs that proteins, cAMP-PKA signal activate eNOS is essential for reducing phosphorylation resistance, and inhibition of NT-region myosin induces activity. Concentration affects release in response to other neurohormones primarily affecting heart function in skeletal muscle. Also, the importance of NT-proBNP modulation in diagnosing patients with various heart conditions is unclear. In conclusion, under LPS stimulation, EP2-PKA signaling can reduce myocardial function by reducing M2 polarization and effective phagocytosis of macrophages.

Experimental Models and Techniques

In this section, the diverse experimental models and techniques used in the study were included to illustrate what certain effects can be induced, which signaling events can be investigated, and whether a relevant signal may transmit between these two experimental models. A critical signal, a delay in experimental time, and an irrelevant experimental model were excluded.

The public research literature uses a variety of experimental models and techniques for the purposes of the study. Both in vitro and in vivo, the experimental technique can focus on separating cardiac and non-cardiac direct effects. The isolated perfused heart model and micro-puncture technique are used to evaluate the direct inotropic and lusitropic effects of experimental agents in cardiac myocytes in this investigation. In a previous study, these techniques were used to investigate the cellular signaling pathways involved in the measured negative inotropic and lusitropic effects in isolated perfused rat myocardium. In the present research, the isolated perfused lung model with Pulmonary Artery Pressure (PAP) measurement as an index for "inflammation" occurrence serves as a very good technical approach. In addition, perfusion pressure was attenuated if endothelial cells were hyper determined in this approach. Macrophage activation can then be analyzed using the "Bronco alveolar lavage" (BAL) technique, whereas the direct effect of experimental agents on lung perfusion was

assessed by dark field microcirculation intravital microscopy in the "isoflurane anesthetized" rat given the EP2-PKA dylutioner. Although not in the public domain, the indicated methods have been described in detail in Methodology.

In Vivo Models

Regarding the in vivo studies of myocardial function, various strategies have been employed. To evaluate the effect of PGE2 on the cardiac function, some researchers have adopted in vivo experimentations with mice subjected to the administration of an EP2 agonist as well as intravenously injected with poly I:C to induce the inflammatory response. The EP2 agonist was also supplied to transgenic mice without myocytes, and isolated macrophages solution applied to evaluate the function of macrophages.

Other studies, focusing more on the clinical aspect of patients having an inflammatory disease at the heart level, could perform the sampling of human biopsies (Takotsubo disease) as well as mice. The mice were injected with LPS to induce an increase in the percentage of peripheral white blood cells, and subsequently sacrificed for ventricular macrophages isolation to evaluate their activation markers. In addition, in order to focus the attention on the "activation of signaling by G protein-coupled receptor (GPCR)", other in vivo models have been used. The innervation of cardiomyocytes induced by vagus nerve has been performed, and to deactivate the potential role by its basal activity, atropine by blocking vagus directly at the heart level was injected to prevent hyperactivation of myocytes. In addition, adult mouse cardiomyocytes were stimulated with the mode of contraction and relaxation, which is with and without the prior t-tubule stimulation.

In Vitro Models

As in vivo studies are limited, several in vitro models have been performed to explain the mechanisms of the contribution of EP2-PKA signaling in cardiomyocytes to the reduction of myocardial function. Research on the molecular mechanisms underlying these phenomena has expanded in various controlled laboratory environments. Some basic experimental models have been used to investigate EP2-PKA signaling in the deterioration of myocardial function in detail. They include a simple model with separated cell types and a multicellularity model. A separated cell type model was developed to analyze the direct effects of culture media derived from other modulator cells on the target cell. The culture medium of stimulated cardiomyocytes suppressed intracellular Ca2+i transient amplitudes and the protein expression of α-actinin in the culture medium of cardiomyocytes.

A similar synergistic contribution of cardiomyocytes has been demonstrated using an in vitro model with handheld or transwell co-culture of macrophages and cardiomyocytes. This co-culture model traced the simultaneous adverse effects of the treatment of agonists of interleukin-one β (IL-1β), protein kinase A inhibitor (PKAi), or E type prostanoid 2 prostaglandin receptor (EP2) to cardiomyocytes. These studies indeed provided the novel evidence to explain the downstream effects of activated macrophages on the EP2-PKA signaling in murine HL-1 atrial cardiomyocyte cell.

Research Article DOI: 10.18081/2333-5106/015-12/769-779

Experiments on this perilous communication of the in vitro macrophage co-culture using the murine or human cardiomyocytes are promising in exploring the molecular or cellular targets. In neighboring cells of non-myocyte, crosstalk was documented in human cardiomyocytes to mediate inflammation-associated arrhythmia using human induced pluripotent stem cell (hiPSC) myocyte monoculture models.

Clinical Implications and Therapeutic Targets

A comprehensive understanding of how myocardial function is reduced during acute and chronic diseases due to the interaction between cardiomyocytes and immune cells, especially through the sePSII pathway, should one day provide novel aspects and implications for clinical treatment. As follows, we offer 2 novel directions towards this concept.

6. Clinical Implications and Therapeutic Targets Elevated levels of prostaglandin E2 (PGE2) via cyclooxygenase (COX) are commonly found during acute inflammation and sepsis, and are often positively associated with outcomes. PGE2 is synthesized by mPGES1/2, produced by immune cells that play critical roles in the pathological homeostasis of the heart during the pathological setting (E,p), and adopt its IP receptor for the IP receptor of cardiomyocytes to allow platelet agonist to improve their prognosis for doctors with poor cardiocyte release of IP2. And PGE2 is mediated by EP2 signaling for the myocardium, which may also act directly to reduce the cell immune response and further reduce the TNFα HSC-CM culture infection of the tooth virus to release EV-Carp (Figure 2) in systemic inflammation. Cardiocyte death also helps immunity at the same time. The clinical relevance of these findings can be tested in clinical trials in infected patients. They have shown that 730 patients experienced severe side effects of EV-D68 infection. If this is correct, mediation of the rate-limiting enzyme mPGES-1, which controls the local population of infected populations, may reduce the level EV-D68 reactivity and improve the patient's survival and prognosis.

Moreover, with the development of molecular biological technology, targeted genetic changes, small interfering RNA technology, shRNA technology, and drug inhibitors have expanded the scope of clinical and pharmaceutical use. Our findings indicate that the reduction in myocardial function may be reduced by influencing the signaling of EP2-PKA. Downstream of PDE4D could prevent the release of R-canabinoid-1.

And the receptor subunit PKA antibody on bone marrow monocyte removal of A-MK, reducing the release of such intravenous flow in mice, comforts and is available for monotherapy in wild-type mice. This suggests that the upstream of R-canabinoid-1 could be a potential therapeutic target for reducing release to relief and myocardial reverse function. Preliminary studies have shown that the IPNK signal could be dissociated by the 37 and 400 chemicals of CE, spopic A l and astayah inhibit PDE4D. Itcwatu homespully events in children and adults portend poor consequences and are usually the sequela of Scedosporium spp. It causes vegetal nosis. Resident space may affect the myocardium, and the detection of elephants in real time reduces its evil consequences.

Conclusion

In conclusion, arguments were presented throughout this essay that suggested a role for EP2-PKA signaling in the regulation of macrophage activation status and that altered macrophage function contributes to the reduction in myocardial function. Furthermore, the suggestion was made that regulation of macrophage function by EP2-PKA signaling represents a novel downstream signaling pathway to investigate for the potential development of new pharmaceuticals to ameliorate heart disease. Research in the general and heart literature consistently indicates that inflammation can cause reductions of myocardial function. This essay has plausibly suggested a mechanistic pathway for such observations. Exploration and investigation of this pathway further is a critical field for future research within the context of heart disease and represents a promising avenue for the development of novel therapeutics.

There are urgently needed pre-clinical studies to investigate whether treatments impacting the positive inotropic mechanisms occurring in the myocardium result in changes in macrophage activation within this organ. Investigations into changes in macrophage activity in humans taking inotropic medications represent another area of potential future research. Additionally, to further confirm the validity of this mechanistic pathway within the heart, more research in humans with varying severity of heart disease may be necessary. This could allow for the exploration of whether changes in macrophage activity and myocardial function are associated with the severity of heart disease, and access to human tissue could allow for the validation of findings from these animal-based studies.

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.

Open access

This is an open-access article distributed by the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-

commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial.
http://creativecommons.org/ licenses/by-nc/4.0/.

References

1. Aronoff DM, Carstens JK, Chen GH, Toews GB, Peters-Golden M. Short communication: differences between macrophages and dendritic cells in the cyclic AMP-dependent regulation of lipopolysaccharide-induced cytokine and chemokine synthesis. J Interferon Cytokine Res 2006;26(11):827-33. [Abstract/Full-Text]
2. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annu Rev Biochem 2000;69:145–182. [PubMed]
3. Nathan C. Points of control in inflammation. Nature 2002;420:846–885. [PubMed]
4. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res 2012;110(1):159–173.
5. Yona S, Kim K, Wolf Y, et al. Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity 2013;38(1):79–91. [PubMed]
6. Hashimoto D, Chow A, Noizat C, et al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity 2013;38(4):792–804. [PubMed]
7. Hashimoto D, Merad M. Harnessing dendritic cells to improve allogeneic hematopoietic cell transplantation outcome. Semin. Immunol 2011;23:50–57. [PubMed]
8. Kim SH, Serezani CH, Okunishi K, et al. Distinct protein kinase A anchoring proteins direct prostaglandin E2 modulation of toll-like receptor signaling in alveolar macrophages. J Biol Chem 2011;286(11):8875-83. [PubMed]
9. Johansson JU, Pradhan S, Lokteva LA, et al. Suppression of inflammation with conditional deletion of the prostaglandin E2 EP2 receptor in macrophages and brain microglia. J Neurosci 2013;33(40):16016-32. [PubMed]
10. Quan Y, Jiang J, Dingledine R. EP2 receptor signaling pathways regulate classical activation of microglia. J Biol Chem 2013;288(13):9293-302. [PubMed]
11. Lu Y, Zhang Y, Li L, et al. TAB1: a target of triptolide in macrophages. Chem Biol 2014;21(2):246-56. [PubMed]
12. Shie FS, Montine KS, Breyer RM, Montine TJ. Microglial EP2 is critical to neurotoxicity from activated cerebral innate immunity. Glia 2005;52(1):70-7. [PubMed]
13. Jobert G. Barin, Noel R. Rose, Daniela Čiháková. Macrophage diversity in cardiac inflammation: a review. Immunobiology. 2012;217(5):468–475. [PubMed]
14. Takahashi K. Development and Differentiation of Macrophages and Related Cells: Historical Review and Current Concepts. Journal of Clinical and Experimental Hematopathology 2001;41:1.

15. Pollard JW. Trophic macrophages in development and disease. Nat Rev Immunol 2009;9:259. [PubMed]
16. Kai H, Kudo H, Takayama N, Yasuoka S, Kajimoto H, Imaizumi T. Large blood pressure variability and hypertensive cardiac remodeling--role of cardiac inflammation. Circ J 2009;73:2198. [PubMed]
17. Montgomery RR, Booth CJ, Wang X, Blaho VA, Malawista SE, Brown CR. Recruitment of macrophages and polymorphonuclear leukocytes in L:yme carditis. Infect Immun. [PubMed]
18. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci 2008;13:453. [PubMed]

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