Title

P2 purinergic receptors: A key but underexplored player in post-myocardial infarction healing

Authors

Cécile Dufeys[1], Luc Bertrand[1], Christophe Beauloye[1,2,3], and Sandrine Horman[1,*]

Affiliations

[1]Pole of Cardiovascular Research (CARD), Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain (UCLouvain), Brussels, Belgium.

[2]Division of Cardiovascular Intensive Care, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

[3]Division of Cardiology, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

*Corresponding author. Email: sandrine.horman@uclouvain.be Address: Ruelle de la Lanterne magique, 14, B-1348 Louvain-la-Neuve, Belgium

Pathological left ventricular remodeling following myocardial infarction (MI) is a major contributor to the development of heart failure. This process is primarily characterized by a sterile inflammatory response and subsequent fibrosis in the myocardium, involving a complex interplay of cellular and molecular actors. In this issue of the American Journal of Physiology - Heart and Circulatory Physiology, Vinhais da Silva et al. delve into the intricate and underexplored role of P2 purinergic receptors in cardiac healing post-MI (1).

MI remains a leading cause of mortality worldwide, despite advances in reperfusion therapies and pharmacological interventions (2). The progression toward heart failure is largely driven by maladaptive left ventricular remodeling, a multifaceted process involving sterile inflammation, fibrosis, and geometric alterations of the ventricle, ultimately leading to contractile dysfunction (2). This pathological response engages a diverse array of cellular players, including platelets, endothelial cells, immune cells, fibroblasts, and surviving cardiomyocytes (3). Despite extensive research, no specific therapies exist to prevent, or

reverse left ventricular remodeling, primarily due to the complexity of this multicellular response (2).

P2 purinergic receptors constitute a family of membrane receptors that respond to purines and their derivatives. This family is divided into seven ionotropic P2X receptors ($P2X_{1–7}$) and eight G protein-coupled metabotropic P2Y receptors ($P2Y_{1\text{-}2,\,4,\,6,\,11–14}$). These receptors are primarily localized to the plasma membrane, but some, such as $P2X_4$, can also be found in intracellular compartments. While P2X receptors are exclusively activated by adenosine triphosphate (ATP), P2Y receptors respond to ATP, adenosine diphosphate (ADP), uridine triphosphate (UTP), uridine diphosphate (UDP), and UDP-glucose. P2 receptors are widely expressed across tissues and have been implicated in both physiological and pathological processes, displaying either beneficial or deleterious effects depending on the context (4). Given their broad involvement in cellular responses, targeting specific P2 receptor subtypes holds promise for therapeutic intervention, including in cardiovascular diseases.

Following MI, dying cardiomyocytes release large quantities of nucleotides, which serve as potent pro-inflammatory and pro-fibrotic signals by activating P2 receptors on neighboring cells (3). Virtually all cell types involved in post-MI remodeling, including platelets, endothelial cells, resident and circulating immune cells, fibroblasts, adipocytes, and surviving cardiomyocytes, express P2 receptors, underscoring the pivotal role of purinergic signaling in cardiac repair. Despite this, literature on P2 receptors in post-MI heart healing remains scarce. Most current research on P2 purinergic receptors in cardiovascular disease focuses on platelet $P2Y_{12}$ receptors and the use of their antagonists as antithrombotic agents.

Ivanes' research group has a longstanding interest in the $P2Y_{11}$ receptor and previously demonstrated its protective role in dendritic cells, cardiac fibroblasts, endothelial cells, and cardiomyocytes under hypoxic conditions (5-7). In their recent review, Vinhais da Silva et al. provide an integrated perspective on how different P2 receptor subtypes orchestrate the post-MI healing process by modulating the behavior of various cellular players (1). To our knowledge, this is the first review offering a comprehensive and sequential analysis of P2 receptor signaling in the context of post-MI cardiac repair.

The review is structured into two main sections. The first part introduces the concept of pathological left ventricular remodeling and its underlying mechanisms. The authors summarize the fundamental biology of P2 receptors, including their classification, signaling pathways, and roles in cellular homeostasis. This provides essential context for understanding how these receptors influence cardiac repair processes. The second section explores how P2 receptor signaling orchestrates the response of different cell types involved in post-MI healing.

Platelets. Beyond their role in thrombus formation, platelets release pro-inflammatory mediators that modulate early post-MI inflammation (8). The review details how P2 receptors, particularly $P2Y_1$ and $P2Y_{12}$, regulate platelet activation, thrombus stability, and inflammation.

Endothelial Cells. Endothelial dysfunction following MI leads to increased leukocyte recruitment and angiogenesis (8). The authors highlight how $P2Y_2$ and $P2Y_6$ mediate leukocyte adhesion and transmigration, while $P2Y_{11}$ protects against endothelial dysfunction by modulating nitric oxide (NO) bioavailability.

Cardiomyocytes. The review describes how P2 receptors contribute to either cardioprotection or cell death, depending on receptor subtype. $P2X_4$ activation is associated with improved contractility and reduced hypertrophy, whereas $P2X_7$ promotes apoptosis and inflammatory signaling through the NLRP3 inflammasome.

Immune Cells. The role of P2 receptors in regulating neutrophil migration, macrophage polarization, dendritic cell activation, and T cell responses is explored in depth. $P2Y_2$ and $P2Y_{14}$ are implicated in neutrophil chemotaxis, while $P2X_4$ and $P2X_7$ influence macrophage polarization and inflammatory resolution (8).

Fibroblasts. Fibroblasts are central to fibrosis development (8). Vinhais da Silva et al. discuss how $P2Y_2$ and $P2X_7$ drive myofibroblast differentiation and collagen deposition, whereas $P2Y_1$ and $P2Y_{11}$ exert antifibrotic effects by modulating fibroblast activation.

Adipose Tissue. Although less studied, the review touches on the emerging role of P2 receptors in regulating epicardial adipose tissue metabolism and inflammation.

The final section of the review evaluates the therapeutic potential of targeting P2 receptors to modulate post-MI inflammation and fibrosis. The authors propose that selective P2 receptor

agonists or antagonists could be used to fine-tune cellular responses and improve cardiac repair. However, challenges remain, particularly regarding receptor ubiquity, opposing effects across different cell types, and the timing of therapeutic intervention. Currently, only $P2Y_{12}$ receptor antagonists (e.g., ticagrelor, clopidogrel) are clinically used (4), but expanding this approach to other P2 receptor subtypes could open new therapeutic avenues.

In summary, this comprehensive review underscores the pivotal yet underexplored role of P2 purinergic receptors in post-MI pathogenesis. By elucidating the intricate interplay between extracellular nucleotides, P2 receptors, and the various cellular players in cardiac healing, Vinhais da Silva et al. pave the way for novel research and therapeutic strategies aimed at mitigating left ventricular remodeling and improving post-MI outcomes.

Disclosures

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Author Contributions

C.D. and S.H. drafted manuscript; L.B. and C.B. edited and revised manuscript; C.D. and S.H. approved final version of manuscript.

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