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Therapeutic potential of CD73+ mesenchymal stem cells for myocardial infarction and beyond

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Summary. Extracellular adenine nucleotides serve as crucial signaling molecules and influence a broad spectrum of physiological and pathological processes. CD73, the rate-limiting enzyme in the metabolism of extracellular adenine nucleotides, is ubiquitously expressed on various cell types, particularly stem cells. $CD73^+$ mesenchymal stem cells (MSCs) have emerged as promising candidates for therapeutic applications due to their immunomodulatory and pro-regenerative properties. Numerous studies have highlighted the crucial role of CD73 in mediating tissue protection in myocardial infarction (MI). In this review, a brief overview of the cell type-specific expression, regulatory effects of CD73 on MSCs, and proangiogenic and immunomodulatory mechanisms is provided, with a focus on current findings concerning the protective functions of CD73 in the context of MI within the framework of stem cell therapy.

Key words: Mesenchymal stem cells (MSCs), Myocardial infarction (MI), Angiogenesis, Immune regulation

Introduction

CD73, also known as ecto-5′-nucleotidase, is a glycosyl-phosphatidylinositol (GPI)-anchored membrane glycoprotein encoded by the *NT5E* gene and is responsible for hydrolyzing circulating or locally released nucleoside monophosphates into bioactive nucleoside intermediates (Alcedo et al., 2021). CD73 functions as a dimer on the plasma membrane and plays a crucial role in maintaining tissue integrity and promoting recovery following hypoxia, ischemia, and inflammatory injury, particularly in hypermetabolic organs such as the heart and brain (Yang et al., 2018). Notably, CD73 also works essentially to regulate immune cell activation, histiocytic injury, intracellular signal transduction, intercellular communication, and other cellular functions (Minor et al., 2019). Given that increased CD73 expression does not always correlate with increased enzyme activity, understanding the specific mechanisms affecting CD73 expression in these contexts is essential.

Recent studies have identified a subpopulation of $CD73^+$ mesenchymal stem cells (MSCs) with promising therapeutic potential for myocardial infarction (MI). These cells demonstrate significant efficacy in promoting cardiac repair and reducing inflammation. However, further research is essential to elucidate their precise mechanisms of action and optimize their clinical application. This review provides a detailed analysis of CD73, including its expression patterns, regulatory mechanisms, and beneficial effects in MI therapy, emphasizing its role within the context of stem cell therapy.

Significance of CD73 expression

CD73 is ubiquitously expressed and plays crucial roles in numerous aspects of normal physiology, as well as in various disease-associated processes (Minor et al., 2019). It contributes to several tissue-protective mechanisms, such as maintaining the balance between inflammation and immune suppression and regulating vascular permeability by promoting the integrity of the endothelial barrier. CD73 expression is highly diverse and can be found on various cell types and tissues throughout the body. This variability plays a significant role in diverse functions, ranging from immune regulation to cancer progression (Fig. 1).

CD73 expression varies widely across different cell types

CD73 expression varies widely across different cell types and tissues. The expression of CD73 on immune

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cells is a pivotal modulator of the local immune response after injury. CD73 was initially used as a surface marker to identify individual B lymphocyte subpopulations, and approximately 3/4 of adult peripheral blood, spleen, and lymph node B cells and tonsillar B cells express CD73 (Thompson et al., 1987; Airas et al., 1996). Research has revealed that CD73 can also be expressed on resting B cells (Saze et al., 2013; Wu et al., 2019), T lymphocytes, including regulatory T cells (Tregs) (Zhuang et al., 2022), T helper 1 (Th1) cells (Zhang et al., 2022), neutrophils (Eltzschig et al., 2004; Siwapornchai et al., 2020), natural killer (NK) cells (Chatterjee et al., 2014), and macrophages (Bours et al., 2006; Tan et al., 2019). Among adult peripheral blood T cells, approximately 19% of $CD3^+$ cells, 11% of $CD4^+$ cells, and 51% of $CD8^+$ cells are positive for CD73 (Dias et al., 2017). Compared with other T-cell subsets, Th1 cells express higher levels of CD73 and transforming growth factor-β (TGF-β), suggesting that Th1 cells have stronger inhibitory functions than other cell subsets (Zhang et al., 2022). Macrophages may gradually acquire an adenosine-forming phenotype to adjust the outcome of the purinergic cascade on their cell surface by upregulating CD73 expression during an inflammatory event.

Interestingly, the expression of CD73 on immune cells is species-specific. In humans, CD73 is expressed on all mature naïve B cells and on some T-cell subsets, such as innate-like T cells, $CD8^+$ T cells, and memory $CD4^+$ T cells (Doherty et al., 2012; Longhi et al., 2014; Dias et al., 2017; Raczkowski et al., 2018). In mice, CD73 is expressed on B cells that are preferentially expressed in mature class switches and germinal centers on most T cells, including Tregs, NK cells, and peritoneal macrophages (Chatterjee et al., 2014; Tan et al., 2019; Zhuang et al., 2022). Notably, CD73 expression rarely occurs on human Tregs (Schuler et al., 2014; Rissiek et al., 2015), although murine Tregs constitutively express CD73 (Zhuang et al., 2022). In the inflamed joints of patients with arthritis, CD39 is upregulated on T cells, while the expression of CD73 is low (Gordon-Smith et al., 2015; Raczkowski et al., 2018).

CD73 expression on MSCs

In addition to the abundance of CD73 on innate and adaptive immune cells, CD73 is also active on nonimmune cells such as myocytes, neurons, fibroblasts (Minor et al., 2019) and MSCs (Naftali-Shani et al., 2013). CD73 was one of the first cell surface antigens identified on MSCs (Thompson et al., 1987; Airas and Jalkanen, 1996). The general term "immunomodulation" mediated by MSCs varies depending on the expression level of CD73 on MSCs from different sources. CD73 is expressed in a varied subpopulation of MSCs, such as bone marrow (Fujii et al., 2018), adipose tissue (Li et al., 2021), umbilical cord/blood (El Omar et al., 2016), and dental pulp/gingival (Yan et al., 2019; Lynch et al., 2020). Its expression is highly heterogeneous, negatively correlated with extended culture time, and downregulated during the early stages of MSCs differentiation (Li et al., 2021).

The nonuniform expression of CD73 is a ubiquitous

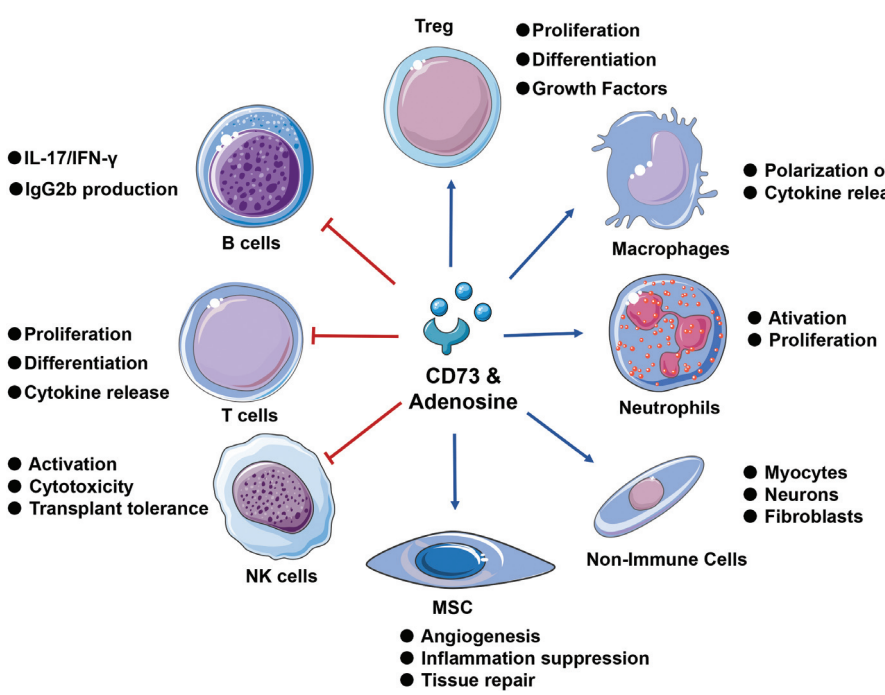

Fig. 1. CD73 expression and activity regulation. The expression of CD73 on different cells is variable and is influenced by external environmental signals. In addition to the abundance of CD73 on immune cells, including B cells, T cells, NK cells, Tregs, macrophages, and neutrophils, CD73 is also active on nonimmune cells, such as myocytes, neurons, fibroblasts, and MSCs. Moreover, the expression and activity of CD73 in MSCs are often influenced by transcriptional regulation, microenvironmental conditions, and interactions with other immune modulators.

phenomenon in the MSCs pool. CD73 expression is rather heterogeneous in MSCs derived from various sources, with the highest expression on MSCs from human umbilical cord blood and the lowest expression on bone marrow-derived MSCs (BMSCs) (Netsch et al., 2018). Our preliminary experimental results also revealed that the expression of CD73 was highly heterogeneous and negatively correlated with culture time and that it was downregulated in the early stage of MSCs differentiation (Li et al., 2021). CD73+ adipose-derived mesenchymal stem cells (ADMSCs) exhibit increased proangiogenic paracrine activity and therapeutic efficacy for MI therapy (Li et al., 2021). The delivery of $CD73^{high}$ MSCs derived from murine pericardial adipose tissue (pMSCs) yields favorable structural and functional benefits and illustrates the crucial role of CD73 in orchestrating cardiac inflammation, in which several anti-inflammatory genes are upregulated while proinflammatory genes are suppressed (Tan et al., 2019).

Functional implications of CD73 expression on MSCs

Based on a series of investigations, CD73 expression and activity regulation are important for maintaining tissue integrity and facilitating recovery after ischemic or inflammatory injury in these cells, especially MSCs. Exploring CD73 regulation in MSCs reveals the multifaceted interplay of mechanisms that are crucial for their immunomodulatory functions. Recent studies have highlighted various factors that influence CD73 expression, including transcriptional regulation, microenvironmental conditions, and interactions with other immune modulators, such as hypoxia-inducible factor-1 (HIF-1) and inflammatory factors. Understanding these dynamics is essential for optimizing the therapeutic applications of MSCs, particularly in regenerative medicine and cardiovascular disease therapy.

Signaling pathways related to CD73 expression in MSCs

CD73 expression is regulated at multiple levels, including transcriptional, posttranscriptional, and posttranslational mechanisms. A recent study (Watanabe et al., 2022) demonstrated that CD73 expression induced by tumor necrosis factor-α (TNF-α)/interferon (IFN)-α stimulation was transcriptionally increased by the activation of mammalian target of rapamycin (mTOR) signaling and the nuclear translocation of HIF-1α in gingival tissue-derived MSCs (GMSCs). In their research, they showed increased CD73 expression by a HIF-1α overexpression plasmid and inhibition of CD73 expression by HIF-1α siRNA under TNF-α/IFN-α stimulation in GMSCs. Furthermore, signal transduction between mTOR-dependent induction of HIF-1 activity and TNF-α/IFN-α-mediated mTOR activation was confirmed by rapamycin treatment of GMSCs, indicating that the mTOR-HIF-1α-CD73 axis is essential for TNF-α/IFN-α-induced CD73 expression in GMSCs (Watanabe et al., 2022). These findings suggest that CD73 is not merely a passive marker of MSCs but also an actively regulated component for the treatment of inflammatory diseases.

Moreover, posttranscriptional modifications, such as mRNA stability and translation efficiency, are also essential for CD73 regulation. Qiu et al. (2023) reported that glioma-associated MSCs-derived exosomal miR-21 promoted CD73 expression through the PTEN/PI3K/AKT/HIF-1α pathway to enhance the immunosuppressive signaling of glioma exosomes, indicating that MSCs-derived exosomes (EXOs) induce CD73 expression on myeloid-derived suppressor cells (MDSCs) in an miRNA-dependent manner. These posttranscriptional mechanisms warrant further investigation as they could provide additional layers of regulation that impact CD73 activity in different pathological contexts.

Regulation of CD73 expression in MSCs

The microenvironment is a critical factor that affects CD73 expression and activity in MSCs. Various studies have shown that disease-associated microenvironments significantly increase CD73 expression. For example, Nakao and colleagues (Nakao and Libby, 2021) not only reported that GMSCs-derived EXOs express CD73 but also reported for the first time that TNF-α pre-conditioning of GMSCs enhances the expression of CD73 on these EXOs. Mechanistically, they speculated that TNF-α induces Rab27 (a family of small GTPases) activation via the nuclear factor κB (NF-κB) pathway to promote EXO release and CD73 expression on GMSCs, thereby yielding a prominent effect. Furthermore, the premetastatic niche is a complex and evolving microenvironment that can be influenced by many systemic and tumor-specific factors (Liu and Cao, 2016). Research has demonstrated (Meade et al., 2019) that secretomes from metastatic breast cancer cells promote a tumor-supportive lung microenvironment with both elevated expression of CD73 and decreased TNF-α expression in MSCs, which, in turn, can mediate the anti-inflammatory effects of metastatic breast cancer cells. These findings highlight the importance of the microenvironment in modulating the immunological functions of MSCs, suggesting that therapeutic strategies should consider the microenvironmental context in which MSCs are deployed.

Interestingly, some studies have shown that the mechanical microenvironment of MSCs can also influence CD73 expression. They reported that TNF-α expression was mechanically upregulated, potentially negatively regulating CD73 expression (Ode et al., 2011). These data corroborate that CD73 activity correlates with mRNA levels in most murine tissues and human cell lines (Hunsucker et al., 2005). However, direct regulation via mechanoresponsive promoter

elements could also be possible (Osmanagic-Myers et al., 2019). This regulatory mechanism raises further questions about the long-term effects of the mechanical microenvironment on CD73 activity and the overall efficacy of MSCs therapies.

Factors affecting CD73 expression

The interplay between CD73 and other immunomodulatory pathways is another area of significant interest. Research has indicated that CD73 can synergize with other immune checkpoint molecules, such as IL-6, TGF-β, EGER, and PKC, to exert more profound immunosuppressive effects. During the progression of nasopharyngeal carcinoma (NPC), MSCs-derived IL-6 transcriptionally upregulates CD73 expression through the activation of the STAT3 signaling pathway, which subsequently binds to the promotor of the *NET5* gene and transcriptionally activates its expression (Zeng et al., 2020). Further studies are warranted to elucidate the complicated interactions or feedback regulatory loops between the IL-6/STAT3 pathway and the CD73-adenosine axis and their contributions to the pathogenesis, immune surveillance, and progression of NPC. Recent studies have shown that CD73 expression and adenosine generation by MSCs and effector T cells are upregulated by TGF-β (Ávila-Ibarra et al., 2019; Chen et al., 2019). Ávila-Ibarra et al. (2019) provided evidence that cervical cancer (CeCa) cells cocultured with CeCa-MSCs were induced to significantly increase CD73 expression via the production of transforming growth factor-β1 (TGF-β1), since the addition of anti-hTGF-β neutralizing antibodies strongly reversed CD73 expression in tumor cells. Tu and colleagues reported that CD73 expression in non-small-cell lung cancer (NSCLC) is promoted through epidermal growth factor receptor (EGFR)-PKC activation via EGFR signaling, which provides an explanation for the high levels of CD73 in NSCLC with the activation of EGFR mutations (Tu et al., 2022).

However, the nature of these interactions is not yet fully understood, leading to conflicting findings in the literature. These questions emphasize the need for more granular investigations to delineate the specific contexts in which CD73 acts in concert with or independently from these other pathways. Understanding these interactions is critical to developing targeted immunotherapies that exploit the full potential of MSCs while minimizing adverse effects.

Therapeutic mechanisms of CD73⁺ MSCs for MI

Stem cell therapy for ischemic heart disease, especially MI, has gradually replaced traditional treatments to meet the clinical need for myocardial repair (Kim et al., 2015). Two key strategies have been identified to enhance stem cell therapeutic efficacy: (i) augmenting the production of cardioreparative growth factors and cytokines and (ii) optimizing the MI microenvironment by modulating the dysregulated immune response. CD73, one of the first surface markers identified in MSCs, plays a crucial role in the repair of myocardial injury (Thompson et al., 1987; Airas and Jalkanen, 1996). In this context, we explored the function of CD73⁺ MSCs in MI treatment (Fig. 2).

Promoting cardiac repair via the secretion of angiogenic factors

Many ischemic heart diseases, such as MI, myocarditis, and congestive heart failure, are involved in the recovery process from normal hypoxia and a strong

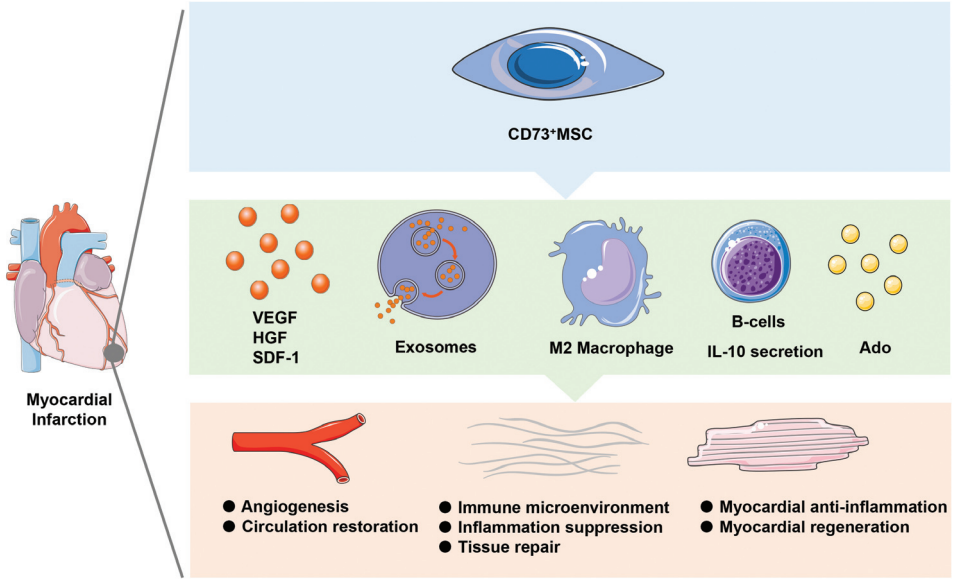

Fig. 2. CD73 functions in MI via stem cell therapy. In MI areas, the activation of CD73⁺ MSCs promotes a variety of protective physiological responses. CD73⁺ MSCs induce immune regulatory effects by stimulating B-cell secretion and the M2 phenotype, optimizing the MI microenvironment. CD73⁺ MSCs also act through the release of bioactive molecules and exosomes and the production of Ado, increasing the production of cardioreparative growth factors and cytokines. These effects contribute to the repair of myocardial tissue in MI.

angiogenic response (Han et al., 2022). The formation of new blood vessels, driven by angiogenesis, is initiated by the activation of dormant endothelial cells via the stimulation of various growth factors, such as VEGF, HGF, SDF-1, PDGF, and FGF. MSCs-secreted factors have been shown to exert angiogenic and antiapoptotic effects on both myocardial and endothelial cells. Two key paracrine factors abundantly secreted by MSCs are VEGF and HGF (Rehman et al., 2004). Recent evidence suggests that CD73, which is expressed on MSCs, significantly enhances the secretion of these angiogenic factors. This will be further discussed in subsequent sections.

Vascular endothelial growth factor (VEGF)

$CD73^+$ MSCs have been shown to facilitate angiogenesis in MI areas by secreting VEGF. Willem van de Veen and his team (van de Veen et al., 2020) reported the same results by studying proangiogenic B cells with angiogenesis-promoting properties in the peripheral blood of melanoma patients and eosinophilic esophagitis patients. This group of B cells induced a greater common duct length and a greater number of connections in the angiogenesis experiment than in the control group. VEGF expression was upregulated in $CD73^+CD49b^+$ B cells compared with that in $CD73^-$ $CD49b^-$ B cells. These authors revealed that the upregulation of CD49b and CD73 surface expression in proangiogenic B cells resulted in increased VEGF expression. This study confirmed the critical role of CD73 and VEGF in promoting angiogenesis. Evidence from $CD73^+$ MSCs provided by Li et al. (Li et al., 2021) revealed that the $CD73^+$ MSCs group presented increased neovascularization density, VEGF expression, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV), as well as enhanced migration ability of human umbilical vein endothelial cells (HUVECs) *in vitro*, compared with the group and other MSCs transplantation groups. The same conclusion was reached by studying adipose MSCs for the treatment of posterior limb ischemia (Kondo et al., 2009) and the secretion of antiapoptotic factors by human adipose stromal cells (Rehman et al., 2004). Although evidence suggests that MSCs promote angiogenesis and treat MI through the PI3K/AKT signaling pathway (Ning et al., 2021; Zhuang et al., 2022), direct evidence linking CD73 to the regulation of this pathway is lacking.

Hepatocyte growth factor (HGF)

HGF is a multifunctional cytokine-containing polypeptide that acts on various epithelial cells and promotes angiogenesis in ischemic cardiac tissue. Research has established that HGF is crucial for the efficacy of MSCs transplantation in enhancing angiogenesis after MI. For example, silencing HGF expression was shown to diminish the angiogenic capacity of mature and progenitor endothelial cells *in vitro* (Cai et al., 2009). Another study revealed that circulating angioblast cells (cMABs) that coexpress endothelial markers in children undergoing cardio-pulmonary bypass (CPB) heart surgery significantly increased HGF when cMABs were most active, and that the injection of recombinant HGF increased the number of cMABs in rats (Iwasaki et al., 2011). Recently, the importance of HGF in MSCs transplantation was further proven in the heart-patch treatment of HGF-expressing MSCs (HGF-eMSCs) for MI (Park et al., 2020). Compared with the other groups, the HGF-eMSCs/BM-MSCs mixed group presented significantly improved left ventricular function, reduced ventricular remodeling, and an increased number of capillaries in the heart boundary area and infarction area (Park et al., 2020). Furthermore, $CD73^+$ MSCs can promote angiogenesis in the MI area by increasing the secretion of HGF (Li et al., 2021). However, the exact molecular regulatory mechanisms remain to be further elucidated.

Stromal cell-derived factor-1 (SDF-1)

In several studies, SDF-1 has been found to play a protective role in promoting angiogenesis in the treatment of MI via MSCs. Huang et al. (Huang et al., 2019) constructed the fusion protein SDF-1-AnxA5, which is composed of SDF-1 and Annexin V (AnxA5, which accurately detects dead cells *in vivo*) domains. SDF-1-AnxA5 has a high binding affinity with the SDF-1 receptor CXCR4, a chemokine receptor that mediates the migration of resting white blood cells and hematopoietic progenitors, and its regulation is related to the ability of SDF-1 to promote the differentiation of MSCs into endothelial cells (Tang et al., 2011). Following establishing an MI model, the injection of SDF-1-AnxA5 significantly reduced the infarct area and improved the LVEF by interacting with CXCR4. *In vitro*, SDF-1-AnxA5 and natural SDF-1 enhanced HUVEC tube formation and promoted neovasculation (Huang et al., 2019). Esmaeili et al. (2021) combined SDF-1 and MSCs in a rat model of MI and revealed that the left ventricular function of the heart after MI improved significantly and that the vascular density increased in the area around the infarction. Furthermore, pretreatment of MSCs with SDF-1 improved their survival in an ischemic environment, further improved cardiac function, and reduced scar size (Esmaeili et al., 2021). Despite these findings, the specific mechanism by which CD73 promotes the production of SDF-1α following stem cell transplantation in MI remains unclear.

Promoting cardiac repair via immune regulation

After MI, dead cardiomyocytes release danger signals to mobilize, recruit, and activate immune cells, triggering an inflammatory response: subsets of monocytes are recruited to the infarct site to help remove

dead cells and stromal debris. Activation of macrophage subsets, mast cells, and lymphocytes can result in fibrotic and angiogenic responses that promote scar formation (Chen and Frangogiannis, 2017). Moreover, an excessive inflammatory response can cause left ventricular remodeling and heart failure (Zhuang et al., 2022). Increasing evidence suggests that CD73 on MSCs can play an immune-regulatory role by regulating immune cells, causing immunoregulatory effects on innate and adaptive immune system cells through cell-cell interactions or derived EXOs or the secretion of soluble factors such as IL-10 and IkDO (Kariminekoo et al., 2016), providing new ideas for the treatment of MI.

Immune cells differentiate from hematopoietic progenitor cells and constitute an important part of the immune system, which includes various lymphocytes and phagocytes (Sender et al., 2023). The regulation of immune cells by MSCs is expected to become a regenerative tool for repairing damaged tissues (Kariminekoo et al., 2016), and the presence of CD73 on MSCs enhances the immunoregulatory effect on some immune cells, making it possible to treat MI-induced injury.

Macrophages

Inflammation plays an important role in the pathophysiological processes of atherosclerosis, plaque formation, and plaque rupture (the main triggers of MI), as well as in myocardial healing and repair after ischemic injury (Tan et al., 2019). The phagocytosis of macrophages to remove dead cells from inflammatory tissue is important for the resolution of inflammation and the restoration of normal tissue function (Gilroy and Maeyer, 2015). Emerging evidence suggests that $CD73^+$ MSCs can contribute to MI treatment by promoting macrophage polarization, limiting inflammatory responses, and regulating immune mechanisms (Monguio-Tortajada et al., 2017; Murphy et al., 2017; Tan et al., 2019; Teo et al., 2023). Research has shown that MSCs derived from pMSCs exist in two populations differentiated by CD73 expression levels, high- and low-CD73 pMSCs (Tan et al., 2019). Transplantation of both types of cells into the injured myocardium after MI has revealed that high numbers of $CD73^+$ pMSCs preferentially lead to structural and functional repair (Tan et al., 2019). Furthermore, $CD73^{high}$ pMSCs reduce $CCR2^+$ macrophage (proinflammatory macro-phage) infiltration and upregulate the expression of several anti-inflammatory genes (*IL-4*, *IL-10*, *arginase-1*, and *TGM-2*) after transplantation of high-CD73 pMSCs *in vivo* and coculture with peritoneal macrophages *in vitro* (Tan et al., 2019). Marta Monguio-Tortajada et al. (2017) reported that MSCs promote the transformation of macrophages from the M1 to the M2 type, as the expression of M2 markers (CD163, CD206, TGM2, and CCL18) increased, whereas the expression of an M1 marker (CD80) remained unchanged. Furthermore, treatment of macrophages with MSCs-derived EXOs *in vitro* significantly increased the expression of CD206 (M2 marker) in macrophages, while there was no change in the expression of the M1 marker (Teo et al., 2023). When M0 macrophages were treated with MSCs-derived EXOs in the presence of CD73 inhibitors, the expression of M2 marker genes (*CD206*, *Arg1*, *CCR1*, *IL-1RN*, *IL-10*, and *PPARγ*) was accordingly reduced (Teo et al., 2023). These findings indicate that $CD73^+$ MSCs-derived EXOs are required for the polarization of M2-like macrophages.

B cells

B cells are generally considered important components of humoral immunity and regulators of innate immunity (Bao and Cao, 2016). Regulatory B cells (Bregs) are B cells with anti-inflammatory functions that play an immunosuppressive role by producing cell membrane-binding molecules such as IL-10, IL-35, TGF-β, CD39, and CD73, which help to limit the sustained immune response and restore immune homeostasis (Rosser and Mauri, 2015). During the progression of MI, overactive inflammatory signaling can exacerbate myocardial damage and cause poor cardiac remodeling. Therefore, timely suppression of pathological inflammation by Bregs is crucial (Wu et al., 2019; Jiao et al., 2021).

Currently, studies on how MSCs-targeted B cells promote MI injury repair are very limited. Research has shown that human placental MSCs inhibit IFN-γ secretion through the CD73/AMPK pathway and promote IL-10 formation in $CD4^+$ T cells (Zhang et al., 2023). Further exploration of the specific signaling pathway by which $CD73^+$ MSCs promote the secretion of IL-10 in B cells to treat MI is warranted. In conclusion, B cells provide a new target for the treatment of MI through the use of CD73+ MSCs to regulate myocardial inflammation.

Promoting cardiac repair through metabolic regulation

CD73 contributes to adenosine production and is an essential component of purinergic signaling. Extracellular Ado is produced in two ways: the first is actively released into the extracellular environment after synthesis by various cells, and the second is produced by degrading extracellular ATP under the synergistic action of CD39 and CD73 (Fig. 3), which can be divided into the canonical and noncanonical pathway. The canonical pathway involves the hydrolysis of ATP to 5'-adenosine diphosphate (ADP) and AMP under the action of CD39, and then Ado is formed under the action of CD73. The raw material in the noncanonical pathway is nicotinamide adenine dinucleotide (NAD^+), which forms ADP ribose through CD38 and is processed into AMP by econucleotide pyrophosphatase/phosphodiesterase family member 1 (NPP1, also known as CD203a), and is ultimately metabolized into adenosine by CD73 (Shin et al., 2018; Galgaro et al., 2021). In particular, CD73 is a

common link between the two Ado pathways and is a key enzyme for Ado production (Chu et al., 2014). In the case of large amounts of ATP released after injury or inflammation, ADP (a key precursor inhibitor of CD73) can significantly inhibit adenosine production but not significantly modulate purinergic signaling in the canonical pathway (Di Virgilio, 2012). Moreover, the noncanonical pathway can compensate for Ado deficiency, which may result from feedforward inhibition of ADP due to the low affinity of ATP for CD203a (Horenstein et al., 2013). Adenosine produced by these two pathways usually has three fates: (i) after extracellular accumulation, it binds to P1 receptors (Ado receptors); (ii) it is activated by ADA; and (iii) it enters the cell through nucleoside transporters (Horenstein et al., 2013). P1 receptors are a family of G protein-coupled receptors that can be divided into four types: A1R, $A2_AR$, $A2_BR$, and A3R (Fredholm et al., 2011). A1R and $A2_AR$ are high-affinity receptors (10 nM-1μM), and $A2_BR$ and A3R are low-affinity receptors (>10 μM). When the receptor is activated, it can cause either inhibition (A1R and A3R) or stimulation ($A2_AR$ and $A2_BR$) of adenylate cyclase, resulting in decreased or increased levels of cAMP, respectively, thereby regulating a variety of intracellular signaling pathways, such as cAMP-dependent protein kinase (PKA) and NF-κB (Galgaro et al., 2021).

Despite the remarkable progress already achieved in considering the adenosine (Ado) pathway as a therapeutic target in different pathologies, its role has not been fully explored in the context of the therapeutic functions of MSCs, especially CD73+ MSCs. Studies have shown that MSCs often release anti-inflammatory cytokines such as PGE_2, TGF-β, and IL-10, which are involved in the regulation of dendritic cells (DCs), NK cells, macrophages, neutrophils, B cells, and T cells (Galgaro et al., 2021). Therefore, the MSCs-mediated conversion of ATP from CD73 to Ado has powerful anti-inflammatory effects and protects the myocardium from excessive inflammatory responses (Galgaro et al., 2021). In DCs, CD73, which acts in combination with its receptor, promotes ATP conversion to Ado through the canonical pathway (Silva-Vilches et al., 2018). The immunosuppressive effect of Ado is mediated by DCs in two ways. First, DC-derived Ado inhibits T-cell activation and promotes the induction of incompetent and/or regulatory T cells in homologous DC/T-cell interactions. Second, Ado from adjacent cells acts on DCs, preventing DC maturation and DC functions (Silva-Vilches et al., 2018). In neutrophils, current evidence indicates that CD73 is the key enzyme that induces Ado production, mainly via the canonical pathway (Haskó and Cronstein, 2004; Lovaszi et al., 2022). Recent experiments have shown that Ado produced in neutrophils regulates immunity in the opposite way by binding to A1R (immune stimulation) and $A2_AR$ (immune suppression) (Lovaszi et al., 2022). Early after injury or infection signals, high concentrations of extracellular Ado facilitate the transition from neutrophil infiltration to DC recruitment to initiate a highly efficient and specific immune response. In the later stages of immune or inflammatory processes, Ado promotes the resolution of inflammation by downregulating macrophage activation and promoting the development of Th2 and Th1 cells (Haskó and Cronstein, 2004; Lovaszi et al., 2022). In NK cells, Ado is also produced via a canonical pathway (Young et al., 2018; Chambers et al., 2018). Ado limits NK cell maturation through the involvement of $A2_AR$ and can affect their proliferation (Young et al., 2018). $A2_AR$-deficient mice in homeostasis presented an increase in the proportion of peripheral mature NK cells

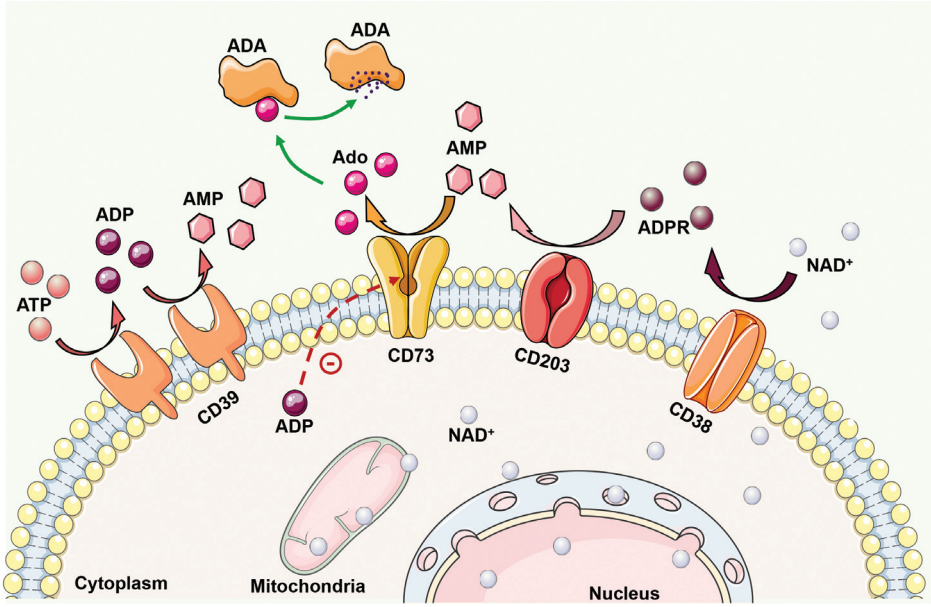

Fig. 3. Pathways of extracellular adenosine (Ado) production and signaling. Ado can be produced from extracellular ATP through the canonical pathway or from NAD^+ via the noncanonical pathway. Canonical pathway: Extracellular ATP is stepwise dephosphorylated by CD39 to produce ADP and AMP. In the noncanonical pathway, AMP can be generated from NAD^+ via the coordinated activity of CD38, which metabolizes NAD^+ to ADPR, and the pyrophosphatase/phosphodiesterase CD203a, which is responsible for the conversion of ADPR to AMP. These pathways culminate in AMP production, which is hydrolyzed by CD73, generating Ado.

(CD11b$^+$CD27) and a corresponding decrease in the proportion of peripheral less mature NK cells (CD11b$^+$CD27$^+$), as well as an accumulation of NK cells expressing the mature markers KLRG1 and Ly49C/I (Young et al., 2018). *In vitro* treatment of NK cells with NECA (a nonselective adenosine agonist that increases the expression of CD73) resulted in decreased proliferation, whereas $A2_AR$ antagonists or *A2AR* gene defects restored the ability of NK cells to proliferate inhibited by NECA (Young et al., 2018), confirming the pivotal role of CD73 in the immune regulation of NK cells (Fig. 4).

Ado can also promote myocardial repair by inducing the release of cytokines. Julia Hesse et al. (Hesse et al., 2017) reported that MI enhances epicardial cell proliferation and stimulates the formation of EPDCs (epicardium-derived cells, which do not take the form of cardiomyocytes or coronary endothelial cells but instead differentiate into MSCs that express fibroblasts and smooth muscle cell markers (Zhou et al., 2011). EPDCs can produce Ado through the action of CD73, which plays a role in promoting MI recovery. A rat model of MI was established, and CD73 expression was also detected in the epicardial layer of the rat heart five days later. A major finding of this study was that EPDCs from post-MI hearts can produce Ado from both extracellular ATP and NAD via the action of CD73 (classical and nonclassical pathways). Ado signaling occurs through $A2_BR$ to stimulate EPDCs to release ATP and NAD from intracellular stores, forming a positive feedback loop. Moreover, it induces the release of cytokines, especially IL-6, IL-10, and VEGF (Hesse et al., 2017). Because EPDCs migrate to the injured myocardium, their paracrine activity can be expected to shape the inflammatory response of the infarcted heart. IL-6, a key cytokine in the tissue response to MI, can inhibit cardiomyocyte apoptosis and control acute inflammatory responses by inhibiting innate immune signaling (Nakao and Libby., 2023). IL-11 can reduce mitochondrial damage, prevent cardiomyocyte apoptosis, and contribute to capillary regeneration at the edge of MI (Allanki et al., 2021). The function of VEGF is described in the section on promoting angiogenesis factors. These effects are beneficial for the recovery of infarcted myocardium.

Conclusion

In short, CD73 plays a role mainly through the canonical pathway to mediate adenosine production in the process of regulating the immune response. By binding to adenosine receptors of immune cells or promoting the secretion of anti-inflammatory cytokines, adenosine then maintains immune homeostasis. This immunoregulatory effect of adenosine is essential for maintaining immune homeostasis and preventing excessive inflammation, which can be detrimental to tissue repair. In the context of MI, CD73 plays a crucial role in promoting tissue repair. By regulating the immune response and reducing inflammation, CD73 helps create a favorable environment for cardiac repair processes, such as the recruitment of stem cells and the formation of new blood vessels. Therefore, targeting CD73 or its downstream signaling pathways could offer promising therapeutic strategies for MI. However, further research is needed to fully elucidate the specific

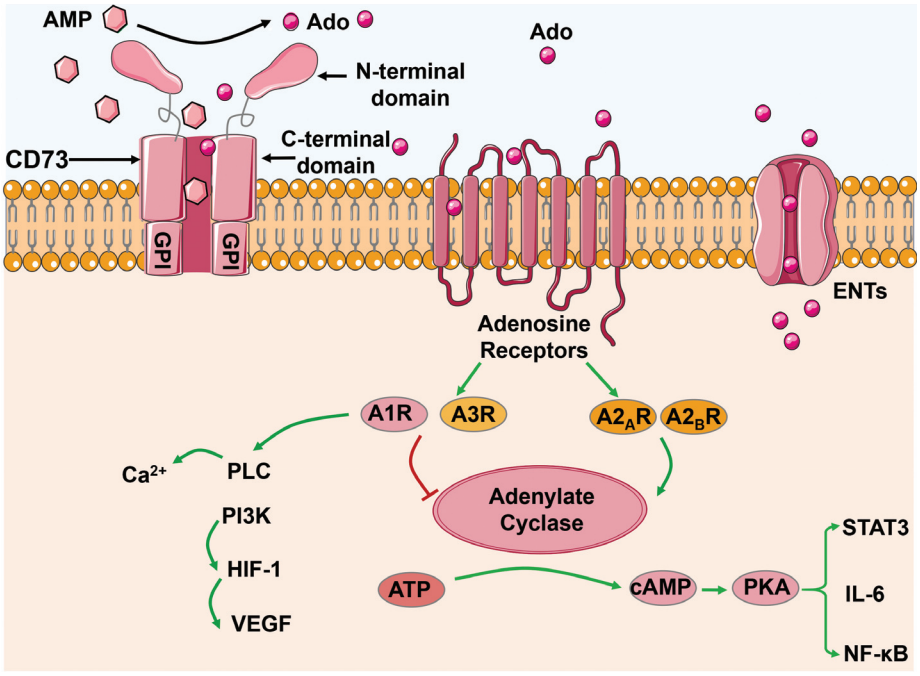

Fig. 4. CD73 molecular and functional properties. As a glycosylphosphatidylinositol (GPI)-anchored ectoenzyme on the plasma membrane, CD73 works in tandem with CD39, which breaks down ATP to form AMP in a two-step process. Extracellular adenosine (Ado) can activate four types of G protein-coupled adenosine receptor (AR): A1R, $A2_AR$, $A2_BR$, and A3R. Adenylate cyclase (AC) is inhibited by A1R/A3R and activated by $A2_AR$/$A2_BR$. ARs can also signal through phospholipase C (PLC), phosphoinositide-3-kinase (PI3K), and protein kinase A (PKA). Alternatively, adenosine can be taken up intracellularly via equilibrative nucleoside transporters (ENTs).

mechanisms by which CD73 mediates cardiac repair and to identify the optimal therapeutic approaches that leverage its effects.

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