Purinergic Signalling (2015) 11:435–440
DOI 10.1007/s11302-015-9466-3

REVIEW ARTICLE

The role of $P2X_7$ receptors in tissue fibrosis: a brief review

Daniela Gentile[1] · Mariarita Natale[1] · Pietro Enea Lazzerini[1] · Pier Leopoldo Capecchi[1] · Franco Laghi-Pasini[1]

Received: 2 June 2015 / Accepted: 18 August 2015 / Published online: 29 August 2015

Abstract Many previous studies have demonstrated that $P2X_7$ receptors ($P2X_7Rs$) have a pleiotropic function in different pathological conditions and could represent a novel target for the treatment of a range of diseases. In particular, recent studies have explored the role of $P2X_7R$ in fibrosis, the pathological outcome of most chronic inflammatory diseases. The aim of this review is to discuss the biological features of $P2X_7R$ and summarize the current knowledge about the putative role of the $P2X_7R$ in triggering fibrosis in a wide spectrum of organs such as the lung, kidney, liver, pancreas, and heart.

Keywords $P2X_7$ receptor · ATP · Inflammation · Fibrotic diseases

Extracellular ATP-mediated purinergic signaling

Purinergic nucleotides and receptors represent a key autocrine/paracrine system for a range of physiological and pathological conditions [1]. Adenosine 5′-triphosphate (ATP) is a major energy molecule contained in all the cells that has an additional role as an extracellular signaling molecule [2]. It is generally accepted that cell damage, mechanical stimulation, hypoxia/ischemia, or pathogen invasion induce ATP release into the extracellular space where it acts as a danger signal representing a defense mechanism in the initial inflammatory phase [3–5]. Once in the extracellular milieu, ATP is rapidly hydrolyzed by two ecto-nucleotidases [6]: CD39 (nucleoside triphosphate diphosphohydrolase-1-NTPDase1) converts ATP to adenosine monophosphate (AMP) and then CD73 (ecto-5'-nucleotidase) converts AMP to adenosine [7]. Although adenosine and its receptors also play a role in the pathogenesis of fibrosis depending on the tissue [8, 9], in this review we will be focusing on the current understanding and advances in the role of $P2X_7R$ in the pathogenesis of fibrosis. ATP signaling is mediated by the family of P2 purinergic receptors (P2Rs), divided into metabotropic P2Y receptors and ionotropic P2X receptors [10]. The metabotropic class are G protein-coupled receptors (GPCRs) that initiate signal transduction coupled to a second messenger; the ionotropic class are cationic ligand-operated channels that upon ATP binding open the pore permeable to Na^+, K^+, and Ca^{++} [11, 12]. Currently, eight subtypes of the P2Y family and seven subtypes of the P2X family have been characterized [13]. P2 receptors are expressed in most cell types; thus, ATP appears to have a crucial and active role in a variety of cell responses including cell proliferation, migration, differentiation, neurotransmission, cytokines release, apoptosis, and necrosis [14]. Nucleotide signaling participates in crucial physiological and pathological events including embryonic development, immune system maturation, neurodegeneration, inflammation, and cancer [15]. $P2X_7R$ may act as a sensor of danger, monitoring the release of the alarm signal ATP at inflammation sites [16].

✉ Daniela Gentile
danielacarmen87@libero.it

Mariarita Natale
natale3@unisi.it

Pietro Enea Lazzerini
lazzerini7@unisi.it

Pier Leopoldo Capecchi
pierleopoldo.capecchi@unisi.it

Franco Laghi-Pasini
laghi@unisi.it

[1] Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Viale Bracci 16, Siena 53100, Italy

$P2X_7R$

The human $P2X_7R$ gene is localized on the long arm of human chromosome 12 (q24.31) and contains 13 exons [17, 18]. The cDNA encodes a protein sequence of 595 amino acids consisting of intracellular N- and C-termini, two hydrophobic transmembrane domains (TM1 and TM2), and an extracellular loop [19]. The N- and C-termini have residues related to selectivity and activity of the ion channel and interact with different membrane proteins including α-actin, receptor-like tyrosine phosphatase, and heat shock proteins [20]. The C-terminal tail is much longer for the $P2X_7R$ than for all the other P2XR family members and is involved in the majority of $P2X_7R$ functions [21]. It is essential for pore formation, receptor stabilization, and signal transduction. Only one α-helix is predicted in the TM1 domain, and a major propensity for β-sheet conformation is expected in the TM2 region. The extracellular loop, with 10 conserved cysteine residues forming disulfide bridges and glycosylation sites represents the ATP binding site [22]. The stoichiometry of $P2X_7R$ involves a trimeric pore that consists of homomultimers [23]. The $P2X_7R$ is predominantly expressed on cells of hematopoietic origin such as monocytes [24], dendritic cells, T and B lymphocytes, eosinophils, mast cells, but also on various types of glia within the peripheral and central nervous system including microglia, astrocytes, oligodendrocytes, and Schwann cells [25, 26]. Moreover, $P2X_7R$ protein is expressed on epithelial cells, osteoblasts, synoviocytes, and fibroblasts [27–30].

$P2X_7R$ has been viewed as a key mediator of inflammation and immunity [31–33], and its pro-inflammatory properties are connected to cytokine release, nitric oxide generation, and cytotoxicity [34]. $P2X_7R$ leads to an amplification of the downstream production of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18, and in turn IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) [35]. Overproduction of these cytokines is detrimental, particularly in chronic disease state [35].

Relationship between $P2X_7R$ and fibrosis

Inflammation is a complex response generated by an interacting network of stimulatory and inhibitory signals. Immune cells primed by soluble factors produced by infections or tissue damage may or may not progress to a full-activated phenotype, depending on the additional signals which they receive from neighboring cells [36]. Ferrari et al. [16] describe $P2X_7R$ like a "sensor of danger" that monitors the release of danger signal, ATP, at inflammation sites and drives mononuclear phagocytes primed bacterial products into fully activated inflammatory effectors (IL-1-secreting cells). When cells are attacked by exogenous pathogens, host cellular receptors recognize pathogen-associated molecular patterns (PAMPs), small molecular motifs conserved among microbes. In many cases, pathogen elimination requires the damage-associated molecular patterns (DAMPs) that include endogenous intracellular molecules released by activated or necrotic cells [37]. PAMPs such as lipopolysaccharide (LPS) can induce the synthesis of pro-inflammatory cytokines such as pro-interleukin (IL)-1β [38], and its release occurs after NALP-3 inflammasome complex activation [39]. Extracellular ATP is a potent DAMP molecule [40] that exerts its effects by binding to the $P2X_7R$ [4]. $P2X_7R$ activation followed by depletion of cytosolic K^+ can drive the assembly of the NALP-3 inflammasome [41, 42]. Once assembled, NALP-3 mediates caspase-1 activation which is then able to cleave pro-IL-1β to its mature form. This cytokine probably by autocrine and paracrine signals upregulates various signaling pathways resulting in an increase of profibrotic transforming factor-β1 (TGF-β1), a central mediator of the fibrotic response in various tissues [43].

Tissue fibrosis resulting from a failure to suppress the normal wound healing response [44–47] is characterized by an increase of fibroblast proliferation and accumulation of extracellular matrix (ECM) proteins leading to organ failure [47]. In vitro studies demonstrate that IL-1β can stimulate collagen expression in a dose-dependent manner [48]. Because IL-1β can induce its own gene expression, chronic activation of the inflammasome resulting in the continual cleavage of IL-1β in a positive feedback mechanism could conceivably maintain a high level of active TGF-β1 protein resulting in fibrosis [49]. In this context, the possibility is raised that $P2X_7R$ may represent a nodal point able to trigger multiple intracellular pathways synergistically activating the collagen biosynthetic machinery. As such, $P2X_7R$ blockade may result in a critical interference in the main pro-fibrotic pathways thus possibly representing an attractive target for the pharmacological modulation of fibrotic diseases.

Lung fibrosis

Pulmonary fibrosis or interstitial lung disease (ILD) includes 130 to 200 fatal chronic lung disorders, characterized by an overgrowth of fibroblasts and ECM deposition resulting in respiratory dysfunction [50]. P2X receptors are expressed in many lung cell types, e.g., type I alveolar epithelial cells [19, 51], pulmonary endothelia, and resident cells of the immune system [3, 52]. $P2X_7R$ has been involved in immune responses initiated by extracellular ATP including lung diseases [53]. Riteau et al. [54] reported extracellular ATP as a danger signal involved in the establishment of lung inflammation and fibrosis via $P2X_7R$ activation on alveolar macrophages. They showed an increased concentration of ATP into the bronchoalveolar lavage fluid (BALF) of patients with idiopathic

pulmonary fibrosis (IPF) as well as into the bronchoalveolar space of murine bleomycin (BLM) model of lung injury. In addition, they evaluated the role of $P2X_7R$ using BLM-treated mice deficient for the receptor reporting a significant reduction in neutrophil recruitment into the BALF as well as in markers of tissue fibrosis such as lung collagen content, matrix-remodeling proteins metalloproteinase-9 (MMP-9), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). Monção-Ribeiro et al. [55] using a model of silica-induced lung fibrosis reported attenuated lung inflammation and fibrosis as well as pulmonary function impairment in silica-exposed $P2X_7$ receptor knockout mice. Either $P2X_7$ receptor knockout or wild-type mice treated with $P2X_7$ receptor inhibitor showed reduced lung inflammation and fibrosis induced by silica. ILD has no effective therapy, and the blockade of the $P2X_7R$ by specific inhibitors in patients with pulmonary fibrosis may be a promising approach to improve their life span.

Renal fibrosis

There is a substantial presence of purinoreceptors in different regions of the nephron, the glomerulus and renal vascular system involved in the regulation of renin secretion, glomerular filtration, and transport of water, ions, nutrients, and toxins [56–59]. The first expression of $P2X_7R$ in renal disease was described in a rat model of diabetes and hypertension [60]. Moreover, Solini and colleagues [61] demonstrated the importance of $P2X_7R$ activation in TGF-β1 secretion and ECM production from mesangial cells. In addition, tubulo-interstitial damage and fibrosis induced after unilateral ureteral obstruction (UUO) are attenuated in the absence of $P2X_7R$. Indeed, $P2X_7R^{(-/-)}$ knockout UUO mice have a lower population of myofibroblasts, diminished collagen deposition, and decreased TGF-β1 expression in the renal interstitium compared to wild-type UUO mice [62]. These data indicate that myofibroblasts may be stimulated by $P2X_7R$ activation either directly, or indirectly in response to cell injury via IL-1β activation which promotes fibroblast proliferation and collagen production. Considered as a whole, these results suggest a crucial role of the receptor in renal inflammation and fibrosis. Thus, the potential use of purinergic antagonists as a tool for novel trials to prevent renal interstitial fibrosis should be considered in the near future.

Hepatic fibrosis

Liver fibrosis refers to the accumulation of fibrous scar tissue caused by the excessive accumulation of ECM [63, 64] by activated hepatic stellate cells (HSCs) [65–67] induced by fibrogenic cytokines such as TGF-β1 [68]. Studies using models of hepatic fibrosis in transgenic mice have revealed IL-1β and TGF-β1 as key players mediating liver fibrogenesis [69, 70]. Huang and colleagues [71] investigated the role of $P2X_7R$ in a mouse model of liver fibrosis induced by carbon tetrachloride (CCl_4), reporting that $P2X_7R$ inhibition with a competitive antagonist (A438079) prevented collagen deposition and also significantly reduced the expression of alpha-smooth muscle actin (α-SMA) and TGF-β1. Finally, in rats affected by common bile duct-ligated (CBDL)-induced liver cirrhosis, Brilliant blue G (BBG), the most potent $P2X_7R$ antagonist in rats, significantly reduces hepatic pro-inflammatory cytokines IL-6, TNF-α, platelet-derived growth factor (PDGF), and IL-1β expression. It also downregulates TGF-β signaling pathway and ameliorates liver fibrosis [72]. These findings suggest the potential application of $P2X_7R$ inhibition in controlling liver fibrogenesis.

Pancreatic fibrosis

Burnstock and Novak reported the implications of purinergic signaling in chronic pancreatitis (CP) [73]. CP is characterized by inflammatory cell infiltration, progressive organ atrophy, and disorganized collagen deposition [74]. Fibrogenesis is also associated with activation of pancreatic stellate cells (PSCs). It has been reported that PDGF and TGF-β1 play key roles in PSC-mediated pancreatic fibrogenesis through autocrine and paracrine loops [75–77]. In the early stage of pancreatic damage, quiescent PSCs undergo a transformation into α-SMA expressing myofibroblast-like cells, which then produce extracellular matrix leading to proliferation and collagen production [78]. In 2012, Haanes et al. [79] showed that PSCs express $P2X_7R$ mRNA and protein. They also showed that both basal and exogenously applied ATP stimulated proliferation of PSCs via $P2X_7R$ [79]. They have suggested that when pancreatic inflammation occurs, the high ATP concentration is used by PSCs to induce IL-1β release, which activates and attracts other PSCs and immune cells. Kunzli et al. [80] showed $P2X_7R$ upregulation in pancreatic tissue samples isolated from patients affected by CP with respect to control samples. Moreover, in a study to understand the impact of CD39 gene deletion using a mouse model of the disease, they noted $P2X_7R$ upregulation [80, 81]. Thus, $P2X_7R$ might be linked with pancreatic remodeling and fibrogenesis.

Cardiac fibrosis

Most cardiac diseases are associated with fibrosis in the heart [82]. The development of cardiac fibrosis is similar to fibrosis in other organs such as the liver, lung, and kidney [83]. Cardiac fibroblasts (CFs) and related myofibroblasts are the principal producers of ECM in response to several growth factors, e.g., TGF-β1, PDGF, and cytokines, e.g., TNF-α, IL-1β, and IL-6 [84, 85]. In the mouse model of acute myocardial

infarction (AMI), Mezzaroma et al. [86] described increased caspase-1 activity and aggregation of three components of the inflammasome—apoptosis speck-like protein containing a caspase-recruitment domain (ASC), cryopyrin, and caspase-1. They demonstrated that the inhibition of cryopyrin or $P2X_7R$, with siRNA in vivo in mice, is sufficient to blunt caspase-1 activation during AMI. In addition, they showed that the prevention of inflammasome assembly using a pharmacological $P2X_7R$ inhibitor, pyridoxalphosphate-6′-azopheny-2′, 4′-disulphonate (PPADS), reduces cell death and adverse cardiac remodeling. The direct implication of the $P2X_7R$ and the upregulation of the NLRP3 inflammasome in CF have been shown in a recent study conducted in mice following myocardial ischaemia-reperfusion (I/R) injury [87] in which silencing $P2X_7R$ in vivo with siRNA has revealed a reduction of the infarct size after myocardial infarction. In keeping with these findings, in vitro data show that myocardial fibroblasts release IL-1β and IL-18 when primed with LPS and subsequently exposed to the danger signal ATP, a molecule that is released in relation to tissue damage during myocardial infarction [87].

Concluding remarks and future prospective

Taken together, these studies offer novel insights into the potential importance of $P2X_7R$ in the fibrotic process of several organs such as the lung, kidney, liver, pancreas, and heart. $P2X_7R$-deficient mice exhibited markedly reduced lung inflammation with reduced fibrosis [54, 55]. $P2X_7R$ promotes macrophage infiltration and collagen deposition contributing to the inflammation and fibrosis of unilateral ureteral obstruction in mice [62]. In accordance, results suggested that $P2X_7R$ activity was present in animal models of liver injury and fibrosis, and contributed to fibrogenesis [71, 72]. Finally, it has been demonstrated that $P2X_7R$ may be a potential target for the treatment of pancreatic [79, 80] and cardiac fibrosis [86, 87]. Although the precise mechanism underlying the involvement of $P2X_7R$ in fibrosis remains unclear and requires further investigation, the receptor seems to be a nodal point in fibrogenesis as an integral component of a pro-inflammatory mechanism. Thus, the potential role of $P2X_7R$ antagonists as a tool for novel trials to prevent fibrosis should be considered in the near future.

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