Computational and Structural Biotechnology Journal 13 (2015) 75–84

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Mini Review

The role of purinergic receptors in stem cell differentiation

Constanze Kaebisch, Dorothee Schipper, Patrick Babczyk, Edda Tobiasch *

Department of Natural Sciences, Bonn-Rhine-Sieg University of Applied Sciences, Von-Liebig-Str. 20, 53359 Rheinbach, Germany

ARTICLE INFO

Article history:
Received 30 August 2014
Received in revised form 31 October 2014
Accepted 3 November 2014
Available online 7 November 2014

Keywords:
P1 receptor
P2 receptor
Purinergic signaling
Regenerative medicine
Adipose tissue-derived stem cells
Bone marrow-derived stem cells

ABSTRACT

A major challenge modern society has to face is the increasing need for tissue regeneration due to degenerative diseases or tumors, but also accidents or warlike conflicts. There is great hope that stem cell-based therapies might improve current treatments of cardiovascular diseases, osteochondral defects or nerve injury due to the unique properties of stem cells such as their self-renewal and differentiation potential. Since embryonic stem cells raise severe ethical concerns and are prone to teratoma formation, adult stem cells are still in the focus of research. Emphasis is placed on cellular signaling within these cells and in between them for a better understanding of the complex processes regulating stem cell fate. One of the oldest signaling systems is based on nucleotides as ligands for purinergic receptors playing an important role in a huge variety of cellular processes such as proliferation, migration and differentiation. Besides their natural ligands, several artificial agonists and antagonists have been identified for P1 and P2 receptors and are already used as drugs. This review outlines purinergic receptor expression and signaling in stem cells metabolism. We will briefly describe current findings in embryonic and induced pluripotent stem cells as well as in cancer-, hematopoietic-, and neural crest-derived stem cells. The major focus will be placed on recent findings of purinergic signaling in mesenchymal stem cells addressed in *in vitro* and *in vivo* studies, since stem cell fate might be manipulated by this system guiding differentiation towards the desired lineage in the future.

Contents

* Corresponding author at: Bonn-Rhine-Sieg University of Applied Sciences, Von-Liebig-Str. 20, 53359 Rheinbach, Germany. Tel.: +49 2241 865 576; fax: +49 2241 865 8576.
E-mail addresses: constanze.kaebisch@h-brs.de (C. Kaebisch), dorothee.schipper@h-brs.de (D. Schipper), patrick.babczyk@h-brs.de (P. Babczyk), edda.tobiasch@h-brs.de (E. Tobiasch).

http://dx.doi.org/10.1016/j.csbj.2014.11.003

1. Introduction

Over the last decades, stem cells have received considerable attention due to their ability of self-renewal and their capacity to differentiate into a wide range of specialized cell types [1]. They have been extensively studied with respect to their applicability for treating a variety of clinical pathologies such as myocardial infarction [2] or critical size bone defects [3]. Especially in the field of tissue reconstruction and transplantation, stem cell-based approaches display a promising tool for which mesenchymal stem cells (MSCs) represent an attractive cell source. Although there are numerous publications illustrating the interaction of extracellular nucleotides and purinergic receptors, little is known about their particular role in embryonic or adult stem cells. Upon binding to their natural ligands purinergic receptors implement a variety of biological actions in many cell and tissue types [4]. Even though it is known that purinergic downstream signaling plays an important role in cellular processes such as proliferation, migration, and differentiation, more detailed insights into these processes are obligatory for the establishment of future clinical applications using the differentiation potential of stem cells without undesired side effects [5]. This review will outline the current state of knowledge on the role of purinergic receptors and their ligands in different pluripotent and multipotent stem cell types with main focus on MSC proliferation and differentiation.

2. Purinergic receptors—structure and distribution

Purinergic receptors are one of the evolutionary oldest receptors [9]. The receptor family can be found in almost every mammalian tissue and was initially described in gut smooth muscle cells in the 1970s[7,8]. In 2014 the first purinergic receptor, namely DORN1, was discovered in plants [6]. Purinergic receptors are divided into P1 receptors which are preferentially activated by adenosine and P2 receptors which are activated by a variety of nucleotides. The latter ones are subdivided into ligand-gated ion channels (P2X) activated by ATP and G-protein-coupled receptors (P2Y) which are activated by nucleotides, di- or triphosphates, purines or pyrimidines (see Fig. 1) [10]. ATP released from cells by several mechanisms e.g. mechanical stimulation is rapidly degraded to adenosine by ectonucleotidases [4]. This ligand receptor system takes part in neurotransmission, mechanosensory transduction, secretion and vasodilatation, as well as long-term signaling functions in cell proliferation, differentiation, and death [4]. Recently, evidence for the functional expression of adenine receptors, designated as P0 receptors, has been found (Fig. 1)[11,12].

2.1. P1 purinoreceptors

P1 receptors are G-protein-coupled receptors expressed in nearly all cell types and take part in a lot of physiological processes within the heart, the cardiovascular system, the nervous system, during inflammation and in pain. Adenosine acts as a natural ligand of P1 receptors and contributes to physiological processes such as cell proliferation and migration in endothelial cells [126]. The P1 receptors are structured into four receptor subtypes named A1, A2A, A2B and A3 and consist of seven transmembrane domains. Next to adenosine they can also be activated and inactivated by various artificial agonists and antagonists (for details see the review of Fredholm et al. [13]). P1 receptor expression in stem cells was reported by different working groups and the understanding of the contribution of these receptors to proliferation and differentiation is increasing [14–16].

2.2. P2 purinoreceptors

2.2.1. P2X receptors

P2X receptors are cation-permeable ligand-gated ion channels which are activated by ATP. Almost every tissue and cell type shows regulated release of ATP mainly via vesicular or conductive mechanisms, whereby the latter ones involve nucleotide transport via hemichannels e.g. pannexins [131]. To date, seven receptor subtypes (P2X1-7) are known that form homomeric (P2X1-5) and heteromeric (P2X2/3 and P2X1/5) receptors, with the exception of P2X6 that cannot form functional homomeric and P2X7 that cannot form functional heteromeric receptors [17,18]. Each subunit consists of two transmembrane domains

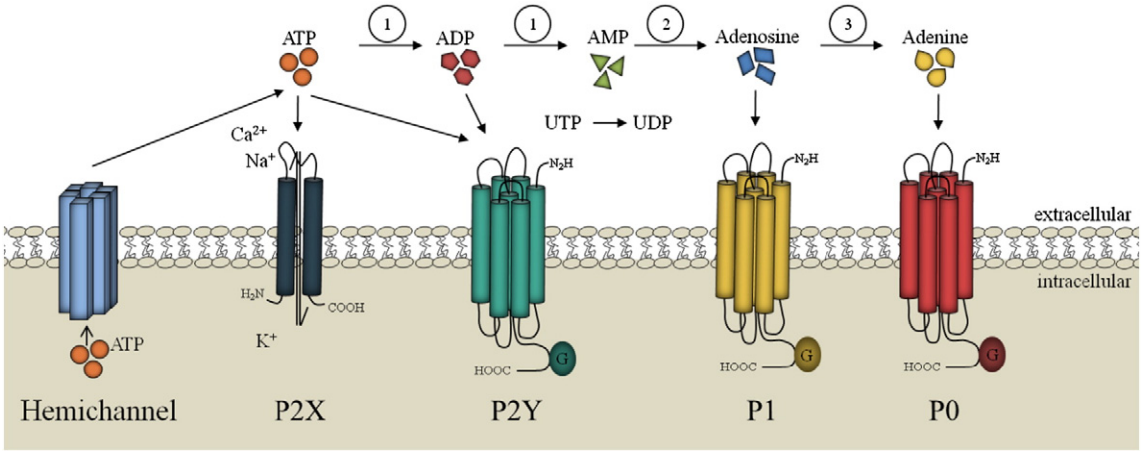

Fig. 1. Purinergic receptors and their natural ligands. Purinergic receptors are divided into P2 receptors which are activated by a variety of nucleotides and can be further subdivided into ionotropic P2X receptors activated by ATP and the metabotropic G-protein-coupled receptors (P2Y) which are stimulated by nucleotides, di- or triphosphates, purines or pyrimidines. In contrast, metabotropic P1 receptors are preferentially activated by adenosine. Recently, evidences for the functional expression of adenine receptors, designated as P0 receptors, have been found. 1: ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases) e.g. CD39, 2: ecto-5'-nucleotidase (CD73), 3: purine nucleoside phosphorylase (PNP).