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Review

Nucleoside transporters in the purinome

Alexandre dos Santos-Rodrigues [a,1], Natalia Grañé-Boladeras [b], Alex Bicket [a], Imogen R. Coe [a,b,*]

[a] Department of Biology, Faculty of Science, York University, Toronto, ON, Canada
[b] Department of Chemistry and Biology, Faculty of Science, Ryerson University, Toronto, ON, Canada

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ABSTRACT

The purinome is a rich complex of proteins and cofactors that are involved in fundamental aspects of cellular homeostasis and cellular responses. The purinome is evolutionarily ancient and is made up of thousands of members. Our understanding of the mechanisms linking some parts of this complex network and the physiological relevance of the various connections is well advanced. However, our understanding of other parts of the purinome is less well developed. Our research focuses on the adenosine or nucleoside transporters (NTs), which are members of the membrane purinome.

Nucleoside transporters are integral membrane proteins that are responsible for the flux of nucleosides, such as adenosine, and nucleoside analog drugs, used in a variety of anti-cancer, anti-viral and anti-parasite therapies, across cell membranes. Nucleoside transporters form the SLC28 and SLC29 families of solute carriers and the protein members of these families are widely distributed in human tissues including the central nervous system (CNS). NTs modulate purinergic signaling in the CNS primarily through their effects on modulating prevailing adenosine levels inside and outside the cell. By clearing the extracellular milieu of adenosine, NTs can terminate adenosine receptor-dependent signaling and this raises the possibility of regulatory feedback loops that tie together receptor signaling with transporter function. Despite the important role of NTs as modulators of purinergic signaling in the human body, very little is known about the nature or underlying mechanisms of regulation of either the SLC28 or SLC29 families, particularly within the context of the CNS purinome. Here we provide a brief overview of our current understanding of the regulation of members of the SLC29 family and highlight some interesting avenues for future research.

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1. Introduction

1.1. Brief overview of the purinome

The purinergic signaling complex of a cell, commonly referred to as the "purinome", is a molecular network of purinergic ligands, receptors, enzymes, channels and transporters (Volonte and D'Ambrosi, 2009). Purinergic signaling is essential in the central nervous system (CNS) and cardiovascular system (CVS), where purinergic ligands, such as ATP and adenosine, act as autocrine and paracrine hormones.

Classically, ATP is considered to be the ubiquitous carrier of chemical energy that drives many chemical reactions in the cell. Evidence of ATP as an extracellular signaling molecule was first observed by Drury and Szent-Györgyi in 1929, when they demonstrated that extracellular ATP and adenosine had effects on heart rate and cardiovascular function (Drury and Szent-Györgyi, 1929). Later, experiments by Holton (1959) demonstrated that ATP release followed antidromic stimulation of sensory nerves in rabbits. The important role of ATP and adenosine in extracellular signaling was corroborated by Ginsborg and Hirst (1972) when they showed that acetylcholine release could be modulated by adenosine. The concept that ATP could act as a neurotransmitter was later inferred from these and other findings by Burnstock in 1972, and this work defined purinergic signaling and regulation as a new and exciting field of study (Burnstock, 1972). Further research has helped to elucidate the role of ATP and adenosine as players in purinergic signaling, but there is still much that remains unknown regarding the interactions between various proteins. There are thousands of distinct proteins that use purines as cofactors, implying that the purinome is diverse, ubiquitous and essential to cellular function (Haystead, 2006).

The purinome is complex and dynamic, and there is a large body of information on the roles of various enzymes and various

* Corresponding author at: Department of Chemistry and Biology, Ryerson University, 350 Victoria St., Toronto, ON M5B 2K3, Canada. Tel.: +1 4169795247.
E-mail address: imogen.coe@ryerson.ca (I.R. Coe).
[1] Current Address: Program of Neurosciences and Department of Neurobiology, Institute of Biology, Fluminense Federal University, Niterói, RJ, Brazil.

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receptors in a wide variety of physiological and pathophysiological contexts (e.g. Burnstock et al., 2011; Coddou et al., 2011; Dale, 2011; Zylka, 2011; Schetinger et al., 2007; Samsel and Dzierzbicka, 2011; Ferrero, 2011; Lane et al., 2011). In contrast, relatively little is known about the members of the purinome that are responsible for the flux of purine nucleosides such as adenosine. The proteins responsible for purine nucleoside flux are the nucleoside transporters. Understanding the role of nucleoside transporters within the larger purinome is important because factors that affect the flux of adenosine (and other purine nucleosides) into and out of cells will have implications on virtually all other aspects of purinergic signaling. Additionally, purinergic signaling is a target of considerable pharmacological interest; therefore understanding the purinome will aid in drug development and drug discovery (Murray and Bussiere, 2009; Knapp et al., 2006), particularly in the CNS and the CVS. Since extracellular concentrations of purinergic ligands can be modulated by both release of ATP and uptake or release of adenosine, a rich regulatory potential for fine-tuning dynamic physiological processes exists in the regulation of nucleoside transporters, and our research focuses on seeking an enhanced understanding of these proteins.

2. Purine nucleoside transporters

2.1. General features of ENTs and CNTs

Nucleoside transporter (NT) proteins are encoded by two different gene families. The SLC28 gene family encodes the concentrative nucleoside transporters, which are Na^+-dependent symporters and which exist in three isoforms (CNT1–3) in humans. CNTs are predicted to possess 13 transmembrane domains with a cytoplasmatic N-terminus and an extracellular C-terminus, and include putative glycosylation sites (e.g. Kong et al., 2004) (Fig. 1a). The other major family of NTs is the SLC29 gene family, the equilibrative nucleoside transporters, which comprise four isoforms (ENT1–4) in humans and which are Na^+-independent passive transporters (Rose and Coe, 2008; Kong et al., 2004; Parkinson et al., 2011). These transporters are also glycosylated, possess 11 transmembrane domains with a cytoplasmatic N-terminus and an extracellular C-terminus. They have a large extracellular loop between transmembrane domains 1 and 2, and a large intracellular loop connecting transmembrane domains 6 and 7 (Sundaram et al., 1998). They have been characterized based on their sensitivity to the nucleoside analog inhibitor, NBTI, with ENT1 being sensitive at nanomolar concentrations, while ENT2 is insensitive at these levels (although sensitive at micromolar concentrations, Parkinson et al., 2011). NBTI interacts with a high affinity binding site through noncovalent interactions on the extracellular side of the protein in the region of transmembrane domains 3–6 (Sundaram et al., 2001a) (Fig. 1b).

ENTs and CNTs transport nucleosides but do not possess obvious sequence or structural similarities, nor is there any structural relationship with other transporter families. NTs are evolutionarily ancient membrane proteins (Sankar et al., 2002) and it is likely that the ENTs have evolved as part of the CNS purinome along with other components, since an ENT homolog is clearly involved in purinergic-dependent associative learning in *Drosophila* (Knight et al., 2010). The ENTs are typically described as being broad spectrum although ENT1 and ENT2 are major contributors to purine nucleoside transport in many tissues. In addition CNT2 and CNT3 transport purine nucleosides, while CNT1 is a pyrimidine-specific transporter. The relative contributions of the ENTs and CNTs to physiological roles of purines continue to be resolved and it is clear the role of nucleoside transporters in the purinome is complex. Many excellent reviews to date have focused on the structure and pharmacological characteristics of both ENTs and CNTs

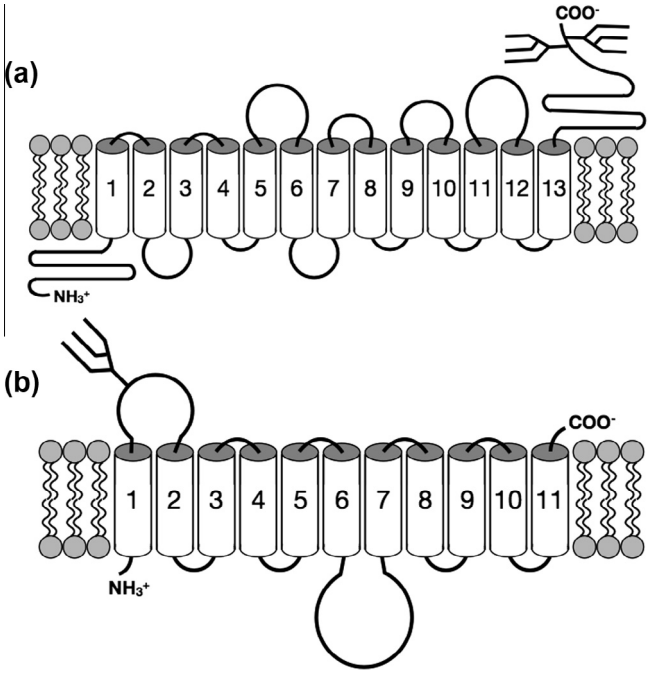

Fig. 1. The proposed 2D topology of concentrative nucleoside transporters (a) and equilibrative nucleoside transporters (b). CNT structure is predicted to have 13 transmembrane domains as well as an intracellular N- and extracellular glycosylated C-termini. ENT structure contains 11 transmembrane domains as well as an intracellular N- and extracellular C-termini. Both proteins are glycosylated (stick structures) and possess large intracellular loops containing numerous putative phosphorylation consensus sites (not shown).

(Parkinson et al., 2011; Young et al., 2008; Kong et al., 2004). However, we continue to face a gap in our understanding of the role and contribution of NTs to the purinome and to purinergic signaling. In this mini-review, we highlight possible future avenues of research into the regulation of ENTs in the CNS.

3. NTs and other members of the purinome

3.1. Main sources of adenosine and crosstalk between members of the purinome

Although all ENTs have been found in the brain (Anderson et al., 1999a,b; Baldwin et al., 2005; Alanko et al., 2006; Dahlin et al., 2007; for a review, see Parkinson et al., 2011), most studies focus on ENT1 and ENT2, since these were the first ENTs to be discovered. ENT3 and ENT4 were described more recently (Kong et al., 2004). Adenosine is a purine nucleoside that is usually described as a neuromodulator, rather than classical neurotransmitter since it has not been shown to be stored in synaptic vesicles. However, some reports suggest that adenosine can be released by similar dynamics to classical neurotransmitter release (Wall and Dale, 2007; Klyuch et al., 2011). Adenosine can also be released from intracellular sites via the ENTs (Wall and Dale, 2013) and possibly via CNT2 (Melani et al., 2012) suggesting that these transporters contribute to both purine nucleoside uptake and to purine release depending on the physiological context. In the CNS, under physiological conditions, ENTs may allow predominantly intracellular to extracellular flux of the purine nucleoside adenosine (for a review, see Latini and Pedata, 2001), particularly in response to glutamate stimulation and in the presence of calcium (Paes-de-Carvalho et al., 2005; Zamzow et al., 2009). In the CVS, ENTs appear to be predominantly responsible for the uptake of extracellular adenosine (i.e. facilitating an extracellular to intracellular flux) and thus

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