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Review

The biochemistry and function of pannexin channels ☆

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ABSTRACT

Three family members compose the pannexin family of channel-forming glycoproteins (Panx1, Panx2 and Panx3). Their primary function is defined by their capacity to form single-membrane channels that are regulated by post-translational modifications, channel intermixing, and sub-cellular expression profiles. Panx1 is ubiquitously expressed in many mammalian tissues, while Panx2 and Panx3 appear to be more restricted in their expression. Paracrine functions of Panx1 as an ATP release channel have been extensively studied and this channel plays a key role, among others, in the release of "find-me" signals for apoptotic cell clearance. In addition Panx1 has been linked to propagation of calcium waves, regulation of vascular tone, mucociliary lung clearance, taste-bud function and has been shown to act like a tumor suppressor in gliomas. Panx1 channel opening can also be detrimental, contributing to cell death and seizures under ischemic or epileptic conditions and even facilitating HIV-1 viral infection. Panx2 is involved in differentiation of neurons while Panx3 plays a role in the differentiation of chondrocytes, osteoblasts and the maturation and transport of sperm. Using the available Panx1 knockout mouse models it has now become possible to explore some of its physiological functions. However, given the potential for one pannexin to compensate for another it seems imperative to generate single and double knockout mouse models involving all three pannexins and evaluate their interplay in normal differentiation and development as well as in malignant transformation and disease. This article is part of a Special Issue entitled: The communicating junctions, roles and dysfunctions.

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1. Introduction

The pannexin family of channel proteins consists of three members, namely Panx1, Panx2 and Panx3. This family of integral membrane proteins was first identified in the mammalian genome in the year 2000 by Panchin and colleagues [1]. Pannexins were discovered due to their limited sequence homology (25–33% identity) to the invertebrate gap junction proteins, innexins (Inxs) [1,2], and were initially proposed to share functional features with the vertebrate gap junction proteins, connexins (Cxs). While no sequence homology exist between Panxs and Cxs all three families of proteins are predicted to exhibit similar topology with four α-helical transmembrane (TM) domains, two extracellular loops (EL), and one intracellular loop (IL), with their amino (NT) and carboxyl (CT) termini exposed to the cytoplasm [1–3] (Fig. 1).

Among the pannexin family members, the NT region is the most highly conserved domain while the highest sequence variability is found in the CT domain [2]. Panx1 and Panx3 are more homologous to each other than to Panx2 [4]. Panx2 exhibits a much larger CT domain that is speculated to convey unique functions to Panx2 regulation, targeting or macromolecular interactions [2]. Additionally, Inxs and Panxs have two cysteine residues in each of their EL domains (Fig. 1) with the exception of *Drosophila* Inx4 that has 3 cysteines in each loop [2,5]. On the other hand, all members of the Cx family (except Cx23 [6]) possess 3 cysteine residues within each EL which form intramolecular disulfide bonds [7].

Analogous to the connexin family of gap junction proteins, initial characterization of Panx1 oligomerization revealed that 6 subunits were required to form a channel [8]. However, similar analysis of Panx2 using a C-terminal truncation mutant revealed that this pannexin most likely assembles into heptamers or octomers [9]. The field is still awaiting an oligomer analysis of Panx3 but given its close polypeptide sequence relationship to Panx1 it is predicted to form hexamers. Recently the substituted cysteine accessibility method was used to identify the pore lining residues of Panx1 channels. This approach revealed that the outer pore structure of Panx1 is lined by portions of the first TM and first EL regions whereas the inner pore lining is contributed by the CT domain and not the NT as it is for connexins [10].

Pannexin oligomers are often called pannexons [8] following the nomenclature established for connexins where oligomers are termed connexons [11,12]. While 'connexons' are also referred to as 'hemichannels' (i.e. a structure constituting half of a cell–cell channel); the term 'pannexons' refers to single-membrane channels. In fact, many authors strongly discourage calling pannexons, hemichannels, as this infers that they are destined to proceed to assemble into an intercellular channel which is not well supported by many recent publications as reviewed by Sosinsky and colleagues [13].

We and others have reported that Panx1 is projected to have a very long half-life [4,14]. The cell surface population of Panx1 remained relatively unchanged when protein secretion was blocked with brefeldin A (BFA) suggesting that this pannexin was not subject to rapid displacement and renewal [4]. In fact, it took up to 32 h of BFA treatment before some clearing of Panx1 from the cell surface was evident with a concomitant increase in newly synthesized Panx1 localized to an ER-like pattern, while clearing of Cx43 from the cell surface was evident within 3 h of BFA treatment (Fig. 2A). This eventual clearing of Panx1 from the cell surface was further correlated with a reduction in the highly glycosylated Gly2 species and an increase in the high-mannose Gly1 species of Panx1 after 20 h of BFA treatment (Fig. 2B). Further evidence that Panx1 is a long-lived molecule was provided as there was a negligible change in the Panx1 species banding pattern upon BFA washout (Fig. 2B).

2. Pannexin expression and genomics

In addition to the human and mouse genomes, the expression of all three pannexin members has now been identified in at least 5 more species including: *Rattus norvegicus* (rat), *Canis familaris* (dog), *Bos taurus* (cow), *Danio rerio* (zebrafish) and *Tetraodon nogroviridis* (puffer fish) [2]. Despite the vast inter-species distribution, pannexins are most well characterized in human and murine tissues. Overall, the human PANX1 (accession number NP_056183, 426 amino acids, 47.6 kDa), PANX2 (accession number NP_443071, 677 amino acids, 74.4 kDa) and PANX3 (accession number NP_443191, 392 amino acids, 44.7 kDa) have conserved sequence homologies of up to 94% with murine pannexins [15].

2.1. Pannexin1 (Panx1)

Various levels of Panx1 are ubiquitously expressed in human tissues such as the brain, heart, skeletal muscle, skin, testis, ovary, placenta, thymus, prostate, lung, liver, small intestine, pancreas, spleen, colon, blood endothelium and erythrocytes, as it was initially reported by Northern blot analysis [3]. Specifically in the central nervous system Panx1 transcripts were detected in the cerebellum, cortex, lens (fiber cells), retina (retinal ganglion, amacrine and horizontal cells), pyramidal cells, interneurons of the neocortex and hippocampus, amygdala, substantia nigra, olfactory bulb, neurons and glial cells [3,16–26]. At the protein level, a tissue survey using custom-designed affinity purified anti-Panx1 antibodies revealed a robust expression of Panx1 in the brain, with variable levels of Panx1 in the lung, kidney, spleen, heart ventricle, skin and sources of cartilage from the ear and tail of 3-week old mice [4]. More recently, Panx1 protein expression was also detected in the rodent cochlea, specifically in supporting cells of the organ of Corti, spiral limbus, cochlear lateral wall, strial blood vessels [27] and in vascular smooth muscle cells of thoracodorsal arteries [28]. In addition, Panx1 has also been reported in the basal compartments of the seminiferous epithelium and epididymis, and in the apical region of efferent ducts of adult rats [29].

2.2. Pannexin2 (Panx2)

In comparison to Panx1, Panx2 mRNA appears more restricted to several areas of the human adult brain including: cerebellum, cerebral cortex, medulla, occipital pole frontal lobe, temporal lobe and putamen [3]. While Northern blot analysis revealed high levels of Panx2 transcript in the rodent brain, spinal cord and eyes, other tissues such as thyroid, kidney and liver revealed low levels of Panx2 transcripts [16–18]. Interestingly, in situ hybridization revealed co-expression of

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