NEURAL REGENERATION RESEARCH
October 2016, Volume 11, Issue 10

www.nrronline.org

INVITED REVIEW

Perspectives on the role of Pannexin 1 in neural precursor cell biology

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How to cite this article: *Sanchez-Arias JC, Wicki-Stordeur LE, Swayne LA (2016) Perspectives on the role of Pannexin 1 in neural precursor cell biology. Neural Regen Res 11(10):1540-1544.*
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Funding: *Research in the Swayne lab was supported by operating grants to LAS from the Natural Sciences and Engineering Research Council of Canada (NSERC Discovery Grant), the Canadian Institutes of Health Research (CIHR Grant MOP142215), The Scottish Rite Charitable Foundation of Canada and the University of Victoria Division of Medical Sciences and by infrastructure grants from the Canadian Foundation for Innovation (CFI) and the British Columbia Knowledge Development Fund (BCKDF). LAS was supported by a Michael Smith Foundation for Health Research and British Columbia Schizophrenia Society Foundation Scholar Award. JCSA was supported by a University of Victoria Fellowship Graduate Award. LEWS was supported by a Vanier Canada Graduate Scholarship (NSERC).*

Abstract
We recently reported that targeted deletion of Pannexin 1 in neural precursor cells of the ventricular zone impairs the maintenance of these cells in healthy and stroke-injured brain. Here we frame this exciting new finding in the context of our previous studies on Pannexin 1 in neural precursors as well as the close relationship between Pannexin 1 and purinergic receptors established by other groups. Moreover, we identify important gaps in our understanding of Pannexin 1 in neural precursor cell biology in terms of the underlying molecular mechanisms and functional/behavioural outcomes.

Key Words: *neural precursor; ventricular zone; pannexin; ATP; cytoskeleton; proliferation; phagoptosis*

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doi: *10.4103/1673-5374.193221*

Accepted: *2016-10-14*

Introduction
Pannexin 1 (Panx1) was discovered in 2000 (Panchin et al., 2000) through moderate sequence homology with invertebrate gap junction forming proteins, the innexins. Although the molecular mechanisms underlying Panx1 activation and modulation have not yet been fully characterized, work from various groups has identified several means, such as membrane depolarization, mechanical deformation and caspase cleavage of the C-terminal tail (reviewed in Chiu et al., 2014). Work in a variety of systems has established that Panx1 facilitates adenosine triphosphate (ATP) release (*e.g.* Bao et al., 2004; Schenk et al., 2008; Ransford et al., 2009), and can pass other ions and metabolites up to 1 kDa in size, likely through its activity as a single membrane channel (Sosinsky et al., 2011). Based on foundational work that ATP is a critical signalling molecule in ventricular zone (VZ) neural precursor cells (NPCs), through the activation of various purinergic (P2) receptors (recently reviewed in Cavaliere et al., 2015), our group investigated and established the expression of Panx1 in VZ NPCs *in vitro* (recently confirmed by Talaveron et al., 2015), where it regulates NPC proliferation, differentiation and migration (Wicki-Stordeur et al., 2012; Wicki-Stordeur and Swayne, 2013). Building on these discoveries, we recently reported our *in vivo* findings on the role of Panx1 in the VZ (Wicki-Stordeur et al., 2016). We deleted Panx1 in NPCs using an approach that consisted of intracerebroventricular injection of control and Cre-recombinase retroviruses co-expressing different fluorescent markers (Tashiro et al., 2006) in Panx1 floxed mice. This strategy allowed us to study NPC "maintenance" since we were able to monitor both Panx1-null and Panx1-expressing NPCs in the same environment over time. Deletion of Panx1 impaired NPC maintenance in the VZ niche, both in healthy and stroke-injured tissue. In contrast, Panx1-null VZ NPCs that had migrated to the peri-infarct cortex exhibited improved maintenance compared with Panx1-expressing NPCs. These results suggest that Panx1 is a key regulator of NPC biology, but there are several outstanding questions with respect to mechanism. For example, does Panx1 influence NPC biology through its channel function (ATP release, ion fluxes), or protein-protein interactions, or a combination of both? While the jury is still out on Panx1 ion selectivity (several reports suggest it is anion-selective, while others suggest it non-selectively passes anions and cations (reviewed in Chiu et al., 2014), we are currently undertaking experiments to investigate how exactly Panx1 regulates NPC biology. Here we review links between Panx1 and the regulation

of NPCs biology from the existing literature. These include interactions with purinergic signalling and interactions with the cytoskeleton, which we outline below. Finally, we conclude with a discussion of another important outstanding question arising from this work: what might be the behavioural implications of Panx1 regulation of VZ NPCs?

Interactions with Purinergic Signalling

Several functional interactions between Panx1 and purinergic signalling have been described (reviewed in Baroja-Mazo et al., 2013) that could be related to this intriguing role of Panx1 in NPCs in the postnatal VZ and peri-infarct cortex (**Figure 1**). Panx1 facilitates the release of ATP and other nucleotides from a variety of cell types (reviewed in Lohman and Isakson, 2014), including NPCs *in vitro* (Wicki-Stordeur et al., 2012). ATP, in turn, binds to P2 receptors to elicit ionotropic (P2X) or metabotropic (P2Y) responses, which have been described to play a role in shaping NPC biology in a variety of ways. This work has been extensively reviewed elsewhere (Zimmermann, 2011; Cavaliere et al., 2015). Moreover, there is a reciprocal regulation of Panx1 by P2 receptors, in which P2 receptor activity elicits Panx1 channel activation, likely through increases in intracellular Ca^{2+} (Locovei et al., 2006; Pelegrin and Surprenant, 2006; Iglesias et al., 2008). Additionally, in certain cell types Panx1 forms a physical association with $P2X_7$ (reviewed in Pelegrin and Surprenant, 2009; Boyce et al., 2014; Chiu et al., 2014). Early reports suggested a role for Panx1 as the large-pore component in the di-phasic activation of $P2X_7$ (Pelegrin and Surprenant, 2006, 2007) but more recent studies found $P2X_7$ large pore activity persisted in the absence of Panx1 (*i.e.*, dye uptake persisted in the $Panx1^{-/-}$ scenario (Qu et al., 2011; Chiu et al., 2014)), suggesting there could be other factors that shape the Panx1/$P2X_7$ relationship that are cell type and/or $P2X_7$ isoform specific.

An intriguing new mode by which purinergic signalling regulates NPC maintenance has recently come to light that we have incorporated into our working model (**Figure 1**). According to this model, it is the expression of different purinergic receptors on different phagocytic cells in the VZ *vs.* the peri-infarct cortex environments that, in effect, "switches" the outcome of a Panx1-mediated ATP signal. In the healthy postnatal VZ, large numbers of NPCs are normally lost (Morshead and van der Kooy, 1992), likely through phagocytic clearance by neighbouring NPCs (Lu et al., 2011). This represents a newly recognized form of cell death known as "phagoptosis", where the inability to display "don't eat me" signals by cells results in their elimination (Brown and Neher, 2012). Phagocytic NPCs are regulated by a non-canonical $P2X_7$-dependant mechanism that is inhibited by extracellular ATP (Lovelace et al., 2015). ATP dissociates the physical interaction between $P2X_7$ and nonmuscle myosin heavy chain IIA, which is essential for the innate phagocytosis/scavenger function of $P2X_7$ as shown both *in vitro* and *in vivo* (Gu et al., 2009, 2010, 2011). These recent findings along with the previously defined role of purinergic signalling in NPC maintenance and differentiation (Cavaliere et

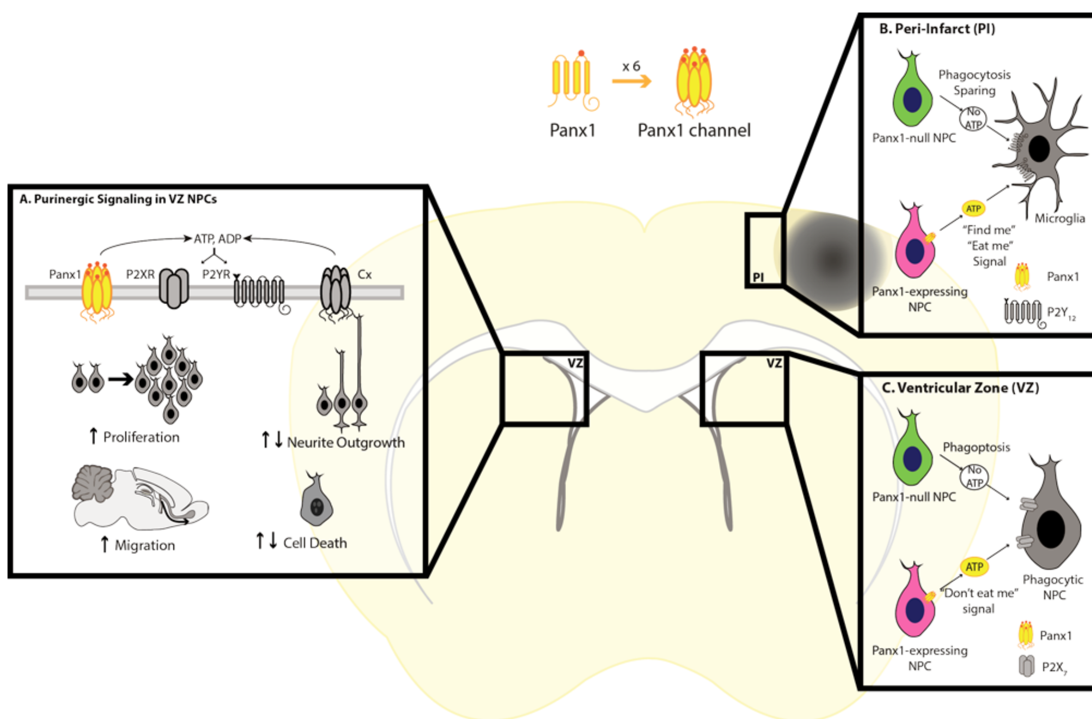

Figure 1 Panx1 interaction with purinergic signalling and role in neural precursor cells (NPCs) in the ventricular zone (VZ) and peri-infarct cortex (PI).
(A) By facilitating adenosine triphosphate (ATP) release, Panx1 interaction with P2 receptors plays critical roles in NPC cellular behaviours. (B) In the peri-infarct cortex, deletion of Panx1 spares NPCs from phagocytic clearance by microglia, a process that involves $P2Y_{12}$ receptors. (C) Within the ventricular zone, phagocytic NPCs with scavenger $P2X_7$ receptors clear local NPCs; this mechanism is inhibited by ATP ("don't eat me" signal) and therefore loss of Panx1 in NPCs makes them susceptible to elimination through "phagoptosis". ADP: Adenosine diphosphate.

al., 2015), suggest that ATP could act as a survival ("do not eat me") signal in the VZ. It has been well established that ATP is episodically released from VZ NPCs (for example see Lin et al., 2007). In our model, we propose that Panx1 represents a major mechanism for episodic ATP release. The model based on our experimental findings proposes that deletion of Panx1 (which facilitates the release of "don't-eat-me ATP) renders NPCs susceptible to clearance *via* phagoptosis (**Figure 1**), accounting for the low number of Panx1 null NPCs observed in the VZ. Conversely, previous work has also shown that in the peri-infarct cortex, ATP acts as a "find-me/eat-me" signal (Patel et al., 2013) through the activation of microglial $P2Y_{12}$ receptors. Therefore, the presence of Panx1 in NPCs that migrated into the peri-infarct cortex would render them vulnerable to phagoptosis (*via* mediating release of ATP, now acting as a "find-me/eat-me" signal). In summary, our model proposes that ATP acts as a "don't-eat-me signal in the VZ, by disrupting physiological $P2X_7$-mediated phagoptosis, while it acts as a "find-me/eat-me" signal in the peri-infarct cortex though activation of metabotropic puringergic receptors on microglia.

Future studies are now needed to address this putative role of Panx1 in regulating phagoptosis of NPCs in the VZ and peri-infarct cortex, as well as establish the precise molecular mechanisms involved in order to determine how this information could be used to strategize treatment paradigms seeking to improve outcomes after a stroke. Our results already suggest that it could be appropriate to target Panx1 in the peri-infarct cortex, perhaps coupling this intervention with other known ways to potentiate NPCs (such as supplementation of growth factors) that have proved to produce objective behavioural improvements in stroke models (Christie and Turnley, 2012). Moreover, the contributions of other ATP-release channels (*i.e.*, LRRC8A, the maxi-anion channel, connexin hemi-channels, and CALHM1 (Sabirov and Okada, 2005; Abascal and Zardoya, 2012; Taruno et al., 2013; Burow et al., 2015)) to phagoptosis could also be investigated.

Interactions with the Cytoskeleton

Apart from the association with purinergic signaling, there are additional possible ways by which Panx1 function could regulate NPC maintenance in the VZ. Foundational work on the cellular and molecular biology of the channel revealed actin is not only critical for Panx1 trafficking and stability in the membrane but also binds directly to its C-terminus (Bhalla-Gehi et al., 2010). Additionally, we also have identified a large number of putative Panx1-interacting proteins in Neuro-2a (N2a) cells using immunoprecipitation coupled to mass spectrometry (Wicki-Stordeur and Swayne, 2013). We validated an interaction between Panx1 and actin, as well as the microfilament-associated protein Arp3 (from the Arp 2/3 complex), and reported that at least 10% of all identified Panx1 protein interaction partners fell under the GO term 'Cytoskeleton' (Wicki-Stordeur and Swayne, 2013). Associations with the cytoskeleton provide stability to plasma membrane populations of Panx1 (Bhalla-Gehi et al., 2010), and likely underlie its mechanosensitive nature (Bao et al., 2004; Seminario-Vidal et al., 2011). Whether Panx1 reciprocally regulates cytoskeleton function in NPCs is unknown; however, in other cell types, ATP released *via* Panx1 modulates actomyosin cytoskeleton dynamics (Bao et al., 2012), and reductions in Panx1 expression alter levels of the intermediate filament protein, vimentin (Penuela et al., 2012). Since cytoskeletal processes are key components of NPC maintenance, regulating behaviours such as cell division and fate specification (reviewed in Lian and Sheen, 2015; Mora-Bermudez and Huttner, 2015), it is feasible to suggest that Panx1 may act, in part, through cytoskeletal remodelling, to affect NPC maintenance. Future studies will investigate the molecular determinants of novel interactions, and explore the potential interplay with channel function.

Given the strong association between Panx1 and proteins involved in cell maintenance, it is notable that we detected no changes in the proliferation of Panx1-null NPCs *via* Ki67 immunoreactivity. Yet, it is possible that Panx1 deletion altered the cell cycle in such a way as to obscure differences in the Ki67 signal (reviewed in Scholzen and Gerdes, 2000). For example, if Panx1 deletion caused cell cycle elongation or stalling within an active phase (G1, S, G2), rather than cell cycle exit (G0), these Panx1-null NPCs would remain Ki67-positive, but possess limited proliferative capacity when compared to their Panx1-expressing counterparts. It is also possible that at the time of our analyses, the small number of remaining Panx1-null NPCs had recovered from, or had become resistant to the effects of Panx1 deletion, perhaps through compensatory mechanisms (Lohman and Isakson, 2014), or normal heterogeneity of gene expression within the NPC population (Johnson et al., 2015). Future studies addressing the role of Panx1 in cell proliferation in NPCs *in vivo* could assess additional cell cycle or proliferation markers (*e.g.* BrdU), alternative time points following Panx1 deletion, and/or analyses of cell cycle length.

Behavioural Implications

Our study raised additional exciting questions. For example, might Panx1 also regulate VZ NPC behaviours during development? A correlation exists between Panx1 expression levels and the proliferative capacity of VZ NPCs, both of which are extremely robust during early brain development and decline with age (Ray et al., 2005; Conover and Shook, 2011). While current Panx1 knock-out models do not exhibit overt defects and can readily reproduce, a recent study reported the first human disease linked to a reduced-function variant of PANX1 (Shao et al., 2016). The affected individual demonstrated significant developmental abnormalities including severe intellectual disability. Although behavioural characterization of constitutive Panx1 knock-out models remains far from exhausted, behavioural dysfunction detected so far includes a tendency to anxiety-related responses and hippocampus-dependent memory impairments, the latter possibly explained by the potently increased long term potentiation (LTP) and reducedlong term depression (LTD) observed in the absence of Panx1 (Prochnow et al., 2012; Ardiles et al., 2014). The contrast between the severe abnormalities found in the human case carrying the reduced-function variant of PANX1 and the constitutive Panx1 knock-out mice could be explained by development of compensatory mechanisms

or redundancy of biological systems (Penuela et al., 2013; Bond and Naus, 2014). Considering the enriched expression of Panx1 in the brain encompasses pyramidal cells and interneurons (especially parvalbumin-positive cells) in the cerebral cortex and hippocampus, as well as Purkinje cells in the cerebellum (Ray et al., 2005; Vogt et al., 2005; Zoidl et al., 2007), generation of conditional and/or inducible Panx1 knock-outs, or knock-in of the reduced-function mutant, will help to enable precise analyses of age- and cell-type dependent effects of Panx1. This includes potentially investigating the effects of Panx1 deletion in hippocampal NPCs. We demonstrated Panx1 expression in hippocampal neurosphere cultures (Wicki-Stordeur et al., 2012), yet this has not been further investigated *in vivo*. In light of the fact that most behavioural abnormalities tested in Panx1 knock-out models are hippocampus-dependent, the implications of Panx1 in hippocampal NPC biology, in health and injury, represents an potentially important area of future study.

It should also be noted that the mouse model used (Dvoriantchikova et al., 2012) in our study also contains a passenger mutation that inactivates caspase-11, also known as caspase-4 and Ich-3 (Vanden Berghe et al., 2015). Because there is virtually no detectable caspase-11 expression in the brain under basal conditions (Wang et al., 1996; Van de Craen et al., 1997), it is difficult to know how this would affect our results in the uninjured control mice where there is not any caspase-11 activation, if it were present, and we see a robust effect of knocking out Panx1. We cannot rule out the possibility, however, that caspase-11 could be upregulated after stroke or other brain injury. That said, a major strength of our experimental paradigm was that it allowed comparison of Panx1-nulll and Panx1-expressing NPCs within the same animal (and therefore same conditions and environment), rather than comparisons between Panxl knock-out and wild type animals on different backgrounds. Still, future studies could examine whether caspase-11 is appreciably expressed or up-regulated in NPCs following brain injury.

We also have yet to determine the behavioural consequences of Panx1 deletion from VZ NPCs. Although the constitutive Panx1 knock-out models have thus far demonstrated few obvious defects, a recent study found impaired olfactory learning in Panx1 deficient mice (Kurtenbach et al., 2014). This is interesting given that adult-born VZ NPCs migrate to the olfactory bulb (OB) in rodents, where they differentiate and specialize into OB interneurons (for review see Lledo et al., 2006; Ming and Song, 2011). Adult-born neurons are also found in the piriform and entorhinal cortices (Shapiro et al., 2009), with the latter sending direct projections to the hippocampus where olfactory and emotional information are consolidated (Kaut et al., 2003). Impaired addition of adult-born neurons to these OB networks results in impoverished odour discrimination and odour-associated perceptual learning (Moreno et al., 2009). It is feasible to suggest that Panx1 deletion from VZ NPCs could similarly reduce addition of OB neurons, given that Panx1 promotes NPC maintenance within the VZ. Thus, behavioural tests directed towards odour discrimination, learning, memory and spatial navigation tasks, in combination with genetic manipulations, may help to determine the functional impact of Panx1 on VZ NPCs.

Concluding Remarks

Panx1 represents a novel molecular player in brain plasticity and neural regeneration thanks to its enrichment in the central nervous system and interactions with purinergic and cytoskeletal signalling. Future studies unraveling molecular mechanisms and investigating its potential role in phagoptosis and animal behaviour will help us to better understand the role of this channel in NPC homeostasis and neuronal development.

Author contributions: *JCSA, LEWS and LAS wrote and revised the manuscript. JCSA created the figure.*
Conflicts of interest: *None declared.*
Author statements: *The present manuscript has not been presented in part or whole at any meeting. It makes references to a variety of scientific reports published in international peer-review journals.*

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