P2X7 is an archaic scavenger receptor recognizing apoptotic neuroblasts in early human neurogenesis

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The expression and function of P2X7 receptors in adult CNS has attracted much study, however, the role of this purinergic receptor in human neural development has largely focused on the effects of receptor activation. Past work on neural stem cells in rodents suggest adenosine triphosphate (ATP), the physiological agonist for P2X receptors, is able to modify proliferation, migration and differentiation, by effects involving intracellular calcium ([Ca2+]i) signaling. The P2X7 receptor has a ubiquitous distribution in the body but is most abundant on macrophages and microglia where its activation by ATP leads to secretion of proinflammatory cytokines. However, extracellular ATP concentrations in the CNS are usually at sub-micromolar levels suggesting that ATP-induced activation of the P2X7 receptor will not occur under physiological circumstances in the CNS. Another possible role for P2X7 receptors has been suggested by recent work on macrophages and neural precursor cells. In these studies the P2X7 receptor was shown to act as a scavenger receptor i.e. a receptor present on a phagocytic cell which detects molecules present on the surface of apoptotic cells and facilitates phagocytosis of the apoptotic cell. In a recent study of human neural precursor cells (hNPCs) and neuroblasts isolated from human fetal telencephalons at 16-19 WG, our group demonstrated that both P2X7R high/DCXlow hNPCs and P2X7R high/DCXhigh neuroblasts had the capability for phagocytic engulfment of a range of targets including latex beads, apoptotic ReN cells and apoptotic neuroblasts. We found that these neuroblasts and their precursor cells expressed functional P2X7 receptors on their cell surface. Although expression of P2X7 is widespread in the cells of the neuroblast, it is those DCX+ neuroblasts with the highest expression of P2X7 which are actively phagocytic towards an autologous apoptotic neighbour or other phagocytic targets, including latex beads and apoptotic ReN cells. Pre-incubation of P2X7+ high neuroblasts with ATP or oxidized ATP inhibited phagocytosis of targets by these cells. Moreover siRNA knockdown of P2X7R also inhibited phagocytosis of the apoptotic targets. This review considers this major new role for the P2X7 receptor in early human neurogenesis.

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PCD plays an essential role throughout organogenesis particularly during early-stage neurogenesis when, if any, neurons have differentiated and the parenchyma is mostly composed of neuroepithelial stem cells, neural precursor cells (NPCs) and proliferating neuroblasts. Estimates suggest that 50-70% of cortical neuroblasts located in the proliferative ventricular zones undergo PCD prior to the later stage of target-dependent synaptic competition (Fig. 1). In contrast, PCD is estimated to account for 20-50% of cell death during the later target-dependent stage of CNS development. PCD of neuroblasts appears to be a universal feature throughout the central nervous system (CNS) and together with the later apoptotic removal of post-mitotic immature neurons, contribute to the essential processes of CNS ‘pruning’ during embryological development.

Role of microglia and astrocytes in target-dependent PCD

Target-dependent PCD is a well-documented stage of the developing nervous system. Neurons in the postmitotic regions that do not establish appropriate synaptic connections die while competing for a limited amount of trophic factors produced by the target cells. Target-dependent PCD and subsequent phagocytosis takes place in the later stages of fetal development and is predominantly mediated by astrocytes and CD68 microglia. Astrocytes are present within the CNS by 14 WG and are capable of engulfing the corpses and debris of cells, thus subserving the important function of innate immune effectors to rid the CNS of cellular debris. Appearing around 16 WG, CD68 microglia also play a major role in the removal of viable neuronal precursor cells, thus regulating the size of the neural precursor cell pool in the developing cerebral cortex.
An equally important process termed target-independent PCD occurs in the earliest-stage of neurogenesis during which apoptotic cells are removed by non-professional phagocytes. In this process, resident neuroepithelial stem cells, their neural precursors and neuroblasts themselves, take up the debris of neighboring apoptotic cells (see Fig. 1). The molecular mechanisms by which apoptotic cells are removed by innate phagocytosis differ from the better studied immunoglobulin and/or complement mediated phagocytosis, and details are slowly emerging.

Mechanisms of Innate Phagocytosis

Innate phagocytosis is the physiological process by which phagocytic effector cells remove apoptotic or non-viable neuronal cells before necrosis ensues. The initial step of phagocytosis requires specific recognition of the apoptotic target by motifs on the surface of the target cell which are highly conserved across different species and cell types. Chief among these is the exposure of phosphatidylserine on the surface of the apoptotic cell although other apoptotic epitopes are increasingly identified such as externalized calreticulin, glycolytic enzymes such as GAPDH or enolase. A defining feature of innate phagocytosis is its non-inflammatory nature and the considerable diversity of cell types capable of engulfing an apoptotic target.

In the late stages of neurogenesis microglia play a major role in the removal of viable precursor cells demonstrating that under normal conditions they can regulate the size of the neural precursor cell pool in the developing cerebral cortex. Astrocytes are also capable of engulfing the corpses and debris of cells, and Lööv et al. recently found that astrocytes protect neurons by engulfing apoptotic cells and play an important role as innate immune effectors to rid the CNS of cellular debris. Others have shown that astrocytes and their glial precursors can phagocytose and eliminate the debris of apoptotic cells both in murine dorsal root ganglia and in later neurogenesis in Drosophila. Even in the absence of these specialized glial cells, cultured neuronal cells could be demonstrated to have phagocytic capacity in vitro towards latex beads and cell debris. More recently Lu et al. showed doublecortin (DCX) positive neuronal progenitor cells had a phagocytic role within the neurogenic zones during adult neurogenesis and the engulfing ability of these progenitors could be demonstrated both in vitro and in vivo.

Neuroblasts with high expression of P2X7 and Doublecortin have the greatest innate phagocytic capability of developing CNS cells

In a major step forward, Lovelace et al. identified the P2X7 receptor as the scavenger molecule expressed on the surface of DCX+ neuroblasts by which these neuroblasts recognize and phagocytose their apoptotic neuronal...
neighbours. Lovelace and colleagues studied cultures of neural precursor cells and neuroblasts isolated from human fetal telencephalon at 16-19 WG and first confirmed the previous observation that DCX is expressed at a lower level on hNPCs but at a higher level on neuroblasts [20]. We then showed these neuroblasts could phagocytose not only autologous apoptotic neuroblasts but also other targets including beads and apoptotic ReN cells. While all cells in the neurosphere expressed P2X7 receptors both on the cell surface and cytosol, we showed by the use of multicolour flow cytometry that the phagocytic effector cells were a subset of DCX+ neuroblasts expressing the highest amount of P2X7 on the cell surface i.e. P2X7\textsuperscript{high}/DCX\textsuperscript{high}. Undifferentiated human neural precursor cells (hNPCs) also have phagocytic capability (see Fig. 2), albeit to a lesser extent than neuroblasts.

Immunostaining of cells from the neurospheres showed widespread positivity for P2X7 receptors. We [21] examined the responses of neuroblasts to ATP and found a dose-dependent elevation in cytosolic Ca\textsuperscript{2+} with increasing ATP concentrations yielding an EC\textsubscript{50} of about 100 nM. These Ca\textsuperscript{2+} responses were reversibly blocked by A438079, a specific antagonist of human P2X7, while the application of L4 functional blocking monoclonal antibody (which recognizes P2X7 ectodomain) also reduced the ATP-mediated responses. These purinergic responses showed the expression of functional P2X7 receptors on the surface of both neuroblasts and their less mature precursors. These data are in line with the established paradigm for this receptor which has the physiological ligand, ATP activating P2X7 on the surface of monocytes and macrophages. This in turn exerts a powerful proinflammatory action from downstream effects including assembly of the NALP3 (NLRP3) inflammasome [22-24]. However there are strong reasons to reject an inflammatory role for this receptor during normal embryonic neurogenesis. Micromolar concentrations of extracellular ATP are required to activate the P2X7 receptor which has an EC\textsubscript{50} of 80-200 µM ATP depending on the presence of divalent cations and the assay used to assess activation [25,26]. Under non-inflammatory conditions, levels of ATP in the cerebrospinal fluid lie in the range 5-15 nM [27] and even luminescent measurements of ATP on the cell surface of cultured astrocytes using membrane-attached luciferase probes give values which remain in the 1-80 nM range [28]. Since ambient ATP rarely reaches the micromolar levels required to activate P2X7, these data raise doubts as to whether P2X7 in the CNS could ever be activated by its ATP ligand except under pathological conditions such as trauma or infection.

**Physiological role and regulation of P2X7 in neurodevelopmental phagocytosis**

![Figure 3](http://www.smartsctech.com/index.php/et/2015; 2: e699. doi: 10.14800/rci.699; © 2015 by Ben J. Gu, et al.)

Figure 3. Two functional conformations of the P2X7-nonmuscle myosin IIA complex either with or without its ATP ligand. In the absence of ATP (left panel) the P2X7 membrane complex is anchored to the actin cytoskeleton via nonmuscle myosin IIA. This conformation of P2X7 functions as a scavenger receptor. When P2X7 is activated (right panel) the ATP ligand opens a cation selective pore and also dissociates nonmuscle myosin from the complex. This conformation leads to formation of the NALP3 inflammasome in microglia and monocyte/macrophages. HSP70 and HSP90 are heat shock proteins while Ro-52 is the 52kDa protein (SS-A) which is the autoantigen found in Sjogren’s syndrome [32].

Other data supports a scavenger function for the P2X7 receptor in the absence of its ATP ligand. Thus P2X7-transfected HEK293 cells or native cells of monocyte-macrophage lineage (which highly express P2X7) can be shown to engulf latex beads, live and dead bacteria and apoptotic cells [29,30]. This phagocytic function for the P2X7 receptor has been recently confirmed by Yamamoto et al. [31] who show that resting astrocytes could engulf latex beads and that this activity was regulated in part by the P2X7 receptor. Immunoprecipitation experiments show P2X7 is present as a multi-protein complex in the plasma membrane of both cultured macrophages and P2X7 transfected HEK293 cells (Fig. 3) [32]. The carboxyl tail of P2X7 has close molecular association with nonmuscle myosin IIA (NMHC IIA) and it is the ATPase activity of this ‘motor’ protein which catalyzes the cytoskeleton rearrangements and membrane cup formation required for particle engulfment. Activation of P2X7 by extracellular ATP causes a conformational change in the receptor which not only opens a cation selective channel/pore but also dissociates P2X7 from the underlying cytoskeleton thereby abolishing its phagocytic function (Fig. 3).

The scavenger activity of P2X7 not only requires the absence of extracellular ATP but also requires a serum-free environment, since as little as 1-5% serum from many animal species and healthy humans completely inhibits innate phagocytosis of apoptotic cells [33] (Fig. 4). Certain glycoproteins in serum including ceruloplasmin, serum amyloid P-component, and amyloid protein precursor are
Figure 4. (A) Representative microscope fields of view of phagocytosis of YG beads by hNPCs/neuroblasts after 1 hour in no serum condition, and (B) in the presence of 5% serum to inhibit phagocytosis. YG beads in green colour are external to the cell, while those coloured yellow have fused with Lysotracker Red-labelled lysosomes. White boxes are enlarged in the yellow zoomed insets to further indicate this. Scale bar in A and B = 25μm. (C) Significant reduction in percentage of cells phagocytosing at least one bead for serum treatment versus non-serum. (D) Frequency distribution of non-phagocytic cells (took up zero beads). Higher numbers of non-phagocytic cells were found with serum treatment (E) Frequency distribution of cells taking up 1-10 beads; substantially higher numbers of beads were phagocytosed in non-serum treated cells. As counted fields contained unequal numbers of total cells, the results in (D-E) have been normalized to 250 cells per field based on the percentage of counted cells in each category. (F) Significantly lower phagocytosis index in serum-treated cells than with no serum treatment (t-test, Mann-Whitney). (G) After fixation and immunostaining, DCX<sup>imm</sup> neuroblasts were found to have phagocytosed significantly more YG beads and had a significantly higher phagocytosis index (H) than hNPCs. Reproduced with permission [21].
responsible for the inhibitory effect of serum on phagocytosis but these glycoproteins are virtually absent from CSF. Thus inclusion of 10-50% CSF in the medium had no inhibitory effect on the phagocytosis of apoptotic neuronal cells by macrophages [55]. These data further support a scavenger role of P2X7 in the phagocytic removal of unwanted apoptotic neurons during early human neurogenesis.

Identity of the Scavenger Receptors

A range of scavenger receptors expressed on the phagocyte plasmalemma have now been implicated in the recognition, binding and ultimate engulfment of the apoptotic target. Within the CNS, including the neural retina, good evidence exists for the role of BAI-1, vitronectin receptors (α,β), αβ5, Jedi-1), and MER receptor tyrosine kinase (MERTK) expressed on microglia or retinal pigment epithelium (RPE) in the clearance of apoptotic cells or photoreceptor discs [17,34,35]. Other candidate scavengers have been proposed as possible candidates including TIM-4, Stabilin-2 and TREM-2 but functional evidence is lacking [36-38]. A new nomenclature and classification has been proposed for scavenger receptors based on structure, consisting of eight major classes each with multiple members [39]. In this classification P2X7 resembles the Class B scavenger topology characterized by two transmembrane domains, a long extracellular loop and both amino and carboxyl termini located within the cytoplasm (Fig. 3). In this group, CD36 is well characterized as a receptor for oxidized phospholipids and has also been implicated in the engulfment of apoptotic cells [40].

How P2X7 recognizes the apoptotic surface of the target cell has been the focus of recent work. P2X7 contains eight cysteine residues in its extracellular domain and modeling based on the crystal structure of zP2X4 [41] shows these are arranged in four disulfide bonds several of which are exposed to the solvent. We have shown that small thiol-reactive compounds such as N-acetylcysteine and glutathione abolish phagocytosis of apoptotic SH-SY5Y cells by macrophages [30]. This feature suggests that P2X7 may bind to the apoptotic surface by thiol-disulfide exchange leading to covalent bonding between phagocyte and target prior to the engulfment step. Cellular interactions dependent on thiol-disulfide have similarity to the scavenger receptor cysteine-rich proteins which are an archaic group of cell surface proteins implicated in metazoan binding of bacteria [42]. Thus, identification of these particular cysteine-containing epitopes on the surface of apoptotic cells which interact with P2X7 or other scavenger receptors would provide us significant insights on the mechanism by which apoptotic cells are recognized and removed. Orthologs of P2X7 have been identified in Teleost fish such as zebrafish and seabream and P2X receptors have appeared early in vertebrate evolution [43]. Our identification of P2X7 as an important scavenger receptor in early neurogenesis of man suggests this functional mode may have important evolutionary implications in vertebrate neurogenesis.

Summary and conclusions

Innate phagocytosis is a critical physiological process in the CNS that removes apoptotic or aged cells and is essential to maintain neurogenesis and avoid neuroinflammation. Engulfment of apoptotic cells by their homotypic neighbours has been previously described in the absence of professional phagocytes [44] and this phenomenon appears widespread in early neurogenesis prior to the appearance of astrocytes and microglia. The binary function of the P2X7 receptor as described by Lovelace et al. suggests that downregulation of inflammatory response and upregulation of innate phagocytic ability could be beneficial to neurogenesis (see Fig. 3 schema). Thus, P2X7, as well as other scavenger receptors, e.g. CD36, MERTK, and their common associated cytoskeletal “motor” protein, nonmuscle myosin heavy chain II [29,45,46], could become promising research and therapeutic targets in neurogenesis.

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Abbreviations

PCD: Programmed cell death; NPC: Neuroblast precursor cell; hNPC: Human neuroblast precursor cell; DCX: Doublecortin; CNS: Central nervous system; NALP3: (NLRP3 or cryopyrin) - Nacht Domain-, Leucine-Rich Repeat-, and PYD-Containing Protein 3 inflammasome; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; NMMHC IIA: Non-muscle myosin heavy chain IIA; MERTK: MER tyrosine kinase.

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