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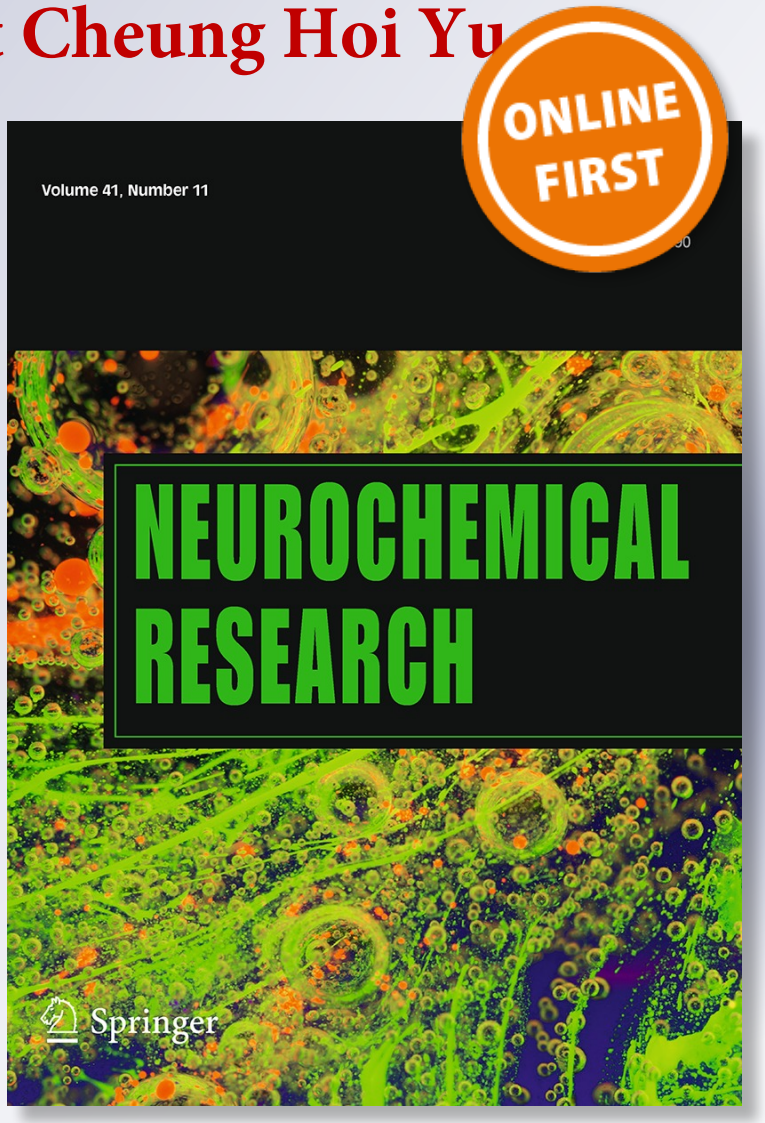

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ORIGINAL PAPER

Astrocytes in Migration

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Abstract Cell migration is a fundamental phenomenon that underlies tissue morphogenesis, wound healing, immune response, and cancer metastasis. Great progresses have been made in research methodologies, with cell migration identified as a highly orchestrated process. Brain is considered the most complex organ in the human body, containing many types of neural cells with astrocytes playing crucial roles in monitoring normal functions of the central nervous system. Astrocytes are mostly quiescent under normal physiological conditions in the adult brain but become migratory after injury. Under most known pathological conditions in the brain, spinal cord and retina, astrocytes are activated and become hypertrophic, hyperplastic, and up-regulating GFAP based on the grades of severity. These three observations are the hallmark in glia scar formation—astrogliosis. The reactivation process is initiated with structural changes involving cell process migration and ended with cell migration. Detailed mechanisms in astrocyte migration have not been studied extensively and remain largely unknown. Here, we therefore attempt to review the mechanisms in migration of astrocytes.

Keywords Cell migration · Astrocytes · Physiological · Pathological · Injury · Reactivation

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Introduction

Cell migration is the central process of development, homeostasis and disease [1]. It is a fundamental phenomenon that underlies tissue morphogenesis, wound healing, immune response, and cancer metastasis [2–4]. Great progresses made in molecular biology, biochemistry, imaging techniques, and advances in genomics and proteomics have identified cell migration as a highly orchestrated process [1]. Central nervous system (CNS) is known to be the most complex system which comprises many types of neural cells. Among these cell types, astrocytes play crucial roles in monitoring normal functions in the aspects of neurotransmitter uptake, synapse formation, regulation of the blood–brain barrier, and development of the nervous system [5–7]. Astrocytes become dynamic migratory cells when they are performing normal physiological action and pathological scar formation. Migration requires a coordination of many events such as actin polymerization, delivery of membrane to

the leading edge, formation of attachment at the leading edge to provide traction, contraction, and disassembly of attachment at the rear. However, the mechanisms of how astrocytes migrate still lack systematic studies. Accumulated evidence has indicated astrocytoma sharing many histological features with astrocytes. Astrocytoma cells infiltrate widely into brain tissues making a complete resection of tumors impossible [8]. Therefore, it might be worthwhile to review the mechanisms involving astrocytes in migration under both physiological and pathological conditions.

Cell Migration in Brain

Cell migration is a crucial process in the developing brain for structural organization [9], and is therefore highly regulated to make sure that the complex networks among neurons and/or glia are right on the beam. Errors during this process may create serious consequences, including intellectual disability, healing problem, tumor formation and metastasis [10]. During CNS development, neurons migrate mainly in two modes: radial and tangential migration [11]. Different types of pyramidal neurons migrate radially to defined positions. In contrast, neurons in rostral migration including gonadotropin-releasing hormone (GnRH) neurons migrate tangentially [12]. The glial family comprises mainly oligodendrocytes, microglia and astrocytes, which have been summarized comprehensively by Garcia-Marin et al. [13]. Oligodendrocyte migration occurs after birth when its progenitors (OPCs, oligodendrocyte precursor cells) migrate from the subventricular zone (SVZ) into the overlying white matter, cortex and deep gray nuclei [14]. In demyelination, OPCs once again become actively proliferative, migratable and differentiable to replenish the lost oligodendrocytes, often leading to spontaneous repair [15]. Microglia are known to be extremely motile. Their motility is especially obvious during brain development where they prune synapses, phagocytize apoptotic newborn neurons, and regulate neuronal activity via direct microglia-neuron or indirect microglia–astrocyte–neuron interactions. These actions all require active cell process motility [16]. Furthermore, microglia are innate immune cells playing pivotal roles in brain injury and neurodegenerative diseases. Microglia cells are usually the first among all cell types in the brain to become highly mobile under various injuries and diseases. Injury-induced microglia cell process movement was slower in the aged as compared to the adult mice [17]. With the focus of this review on astrocytes, researches on cell motility in oligodendrocytes and microglia have been reviewed in other recent publications [18, 19].

Astrocytes in CNS

Astrocytes are certainly the most abundant cell type in the CNS [6]. They were always considered playing only a secondary and passive role in supporting neuronal distribution and interactions. Astrocytes are heterogeneous, composed of radial astrocytes, fibrous astrocytes and protoplasmic astrocytes which differ in morphology, development, metabolism, and cellular physiology [20]. The last several decades of research effort have suggested that astrocytes in fact play active and crucial roles in brain development, functions and information processing during development, adulthood, aging and injury [21]. Phylogenetic analysis indicates that astrocytes have not only become more diverse and specialized, but have also become more essential for neuronal function and survival [20]. For example, Mary McKenna has reviewed the crucial role of astrocytes in glutamate–glutamine cycle which makes it an essential and dynamic partner in both glutamatergic and GABAergic neurotransmission in brain [22]. Moreover, astrocytes are also metabolically involved in synthesis and possible transport of one of the most important neuronal energy substrates—lactate [23]. Their importance in CNS was further demonstrated by their complexity in the human cerebral cortex than those in other mammals [21]. As reported by Oberheim et al. human astrocytes have been shown to be bigger than those in mice, and their engraftment enhances synaptic plasticity and learning in adult mice [24, 25]. These results further reveal that astrocytes might play roles in activity-dependent plasticity and learning with neurons. More interestingly, astrocytes were recently proposed to constitute to an extraneuronal signaling system in CNS [26]. These new findings on astrocytic functions ought to ultimately change our traditional view on the operation of our CNS.

Astrocyte Migration Under Physiological Conditions

Radial glia (RG) are progenitor astrocytes in the SVZ of mammalian embryonic/fetal brains. These cells extend long ascending processes known as radial fibers to the pial surface and act as a scaffold to support the migration of glial progenitors and keep these progenitor cells in an immature and migratory state [15]. These glial progenitors migrate into the cortical gray matter and white matter to differentiate into protoplasmic and fibrous astrocytes respectively [27]. The migration of glial progenitors is involved with retraction of

the radial fibers and elevation of the cell soma from the ventricular zone (VZ), a movement very similar to the "somal translocation" in neuronal migration [28]. Resident glial progenitors are also found in the adult brain, but they are usually not migratory under normal circumstances. They could be activated to become migratory under pathological conditions such as trauma, ischemia, infection, inflammation, and neurodegeneration [29–31].

Astrocytes in adult brain are quiescent under normal physiological condition, but they could influence normal CNS functions through a reversible cell process migration. The thin astrocytic cell processes normally separate neurons in the supraoptic nucleus (SON) of hypothalamus, but could retract to allow glutamate transmission and lactation. These processes would migrate back to their original positions to cut off the transmission at the end of the lactation cycle [32–34]. Whether this is usual for astrocytes to interfere functions of CNS still needs more investigation.

Astrocyte Migration Under Pathological Conditions

Astrocytes are activated in injured and diseased CNS [35]. Injured astrocytes become migratory through a process called astrogliosis. Whether the astrogliosis is beneficial or detrimental remains controversial over the years, however, it did become clear that in the early phase of CNS injury, astrogliosis is a critical and immediately protective response [36]. In later phase of astrogliosis, reactive astrocytes will release harmful chemicals and forming physical barriers to inhibit axonal regeneration [37, 38]. The whole process involves tremendous changes in all aspects of astrocytes. The metabolic alterations as well as the trafficking of metabolites between astrocytes and neurons after injury were recently reviewed by Mary McKenna [39]. Here, we focus on discussing astrocyte migration under pathological conditions.

Numerous complex molecular events occur in astrocytes during cell migration. On the molecular level, astrocytes require a fine spatial–temporal integration of hundreds of proteins that comprise the fundamental processes which drive cell migration [2]. Utilizing various experimental models, considerable advances have been made in understanding the migration processes including the signaling pathways involved and how these may be regulated to achieve specific modes of migration in different conditions.

A Classic Model for Cell Migration Study: Scratch-Wound Assay

In 1993, our laboratory has developed an in vitro model based on a scratch-wound assay to study astrocyte migration and their response to a physical scratch in primary cultures after traumatic injury [40]. Cultures were scratched with a sterile plastic pipette tip according to a grid to mimic injury (Fig. 1). The degree of injury was estimated by comparing the protein content in the scratched cultures to unscratched cultures. Scratching a confluent culture of astrocytes created denuded areas by removing cells from the substratum. Cells along the wound were physically and traumatically damaged to varying degree (Fig. 2). Such model demonstrated scratch damage in a reproducible way. Moreover, by monitoring culture medium immediately following scratch wound, different experimental conditions can be manipulated to study how astrocytes respond to the injury. Changing medium could, to the greatest extent, eliminate most of the debris and factors released from the detached and damaged cells to exclude the exogenous source of stimuli and therefore reflect mostly the intrinsic responses of astrocytes to the scratch [40]. Not changing the medium after scratch however, simulates the actual physical injury conditions, leading to the responses reflecting a combination of both intrinsic and exogenous stimuli [41]. As astrocytes along the scratch exhibit the characteristics of astrogliosis—hypertrophy, hyperplasia, and GFAP increase [42], this model allows one to monitor and investigate the cell process and cell migration under live conditions with time-lapse recording under designed treatments as shown in Fig. 2 [40, 42–44]. Meanwhile, cultures cells can also be immunostained and cells along and away from the scratch can be compared. In addition to our scratch-wound model, other in vitro, ex vivo and in vivo models used for cell migration studies are summarized in Table 1.

Adhesion of Astrocytes

Cell motility requires the formation of attachment at the leading edge providing traction and disassembly of

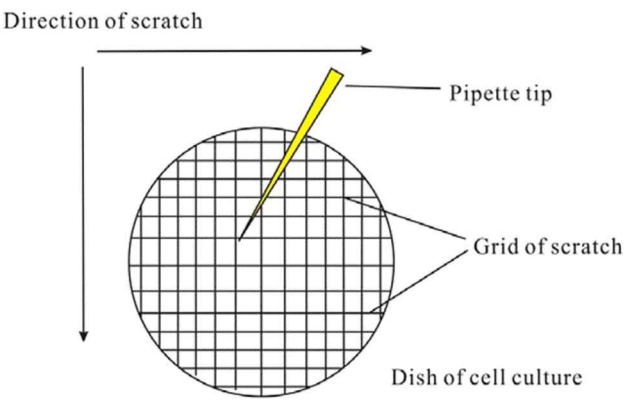

Fig. 1 Scratch wound of primary culture of astrocytes

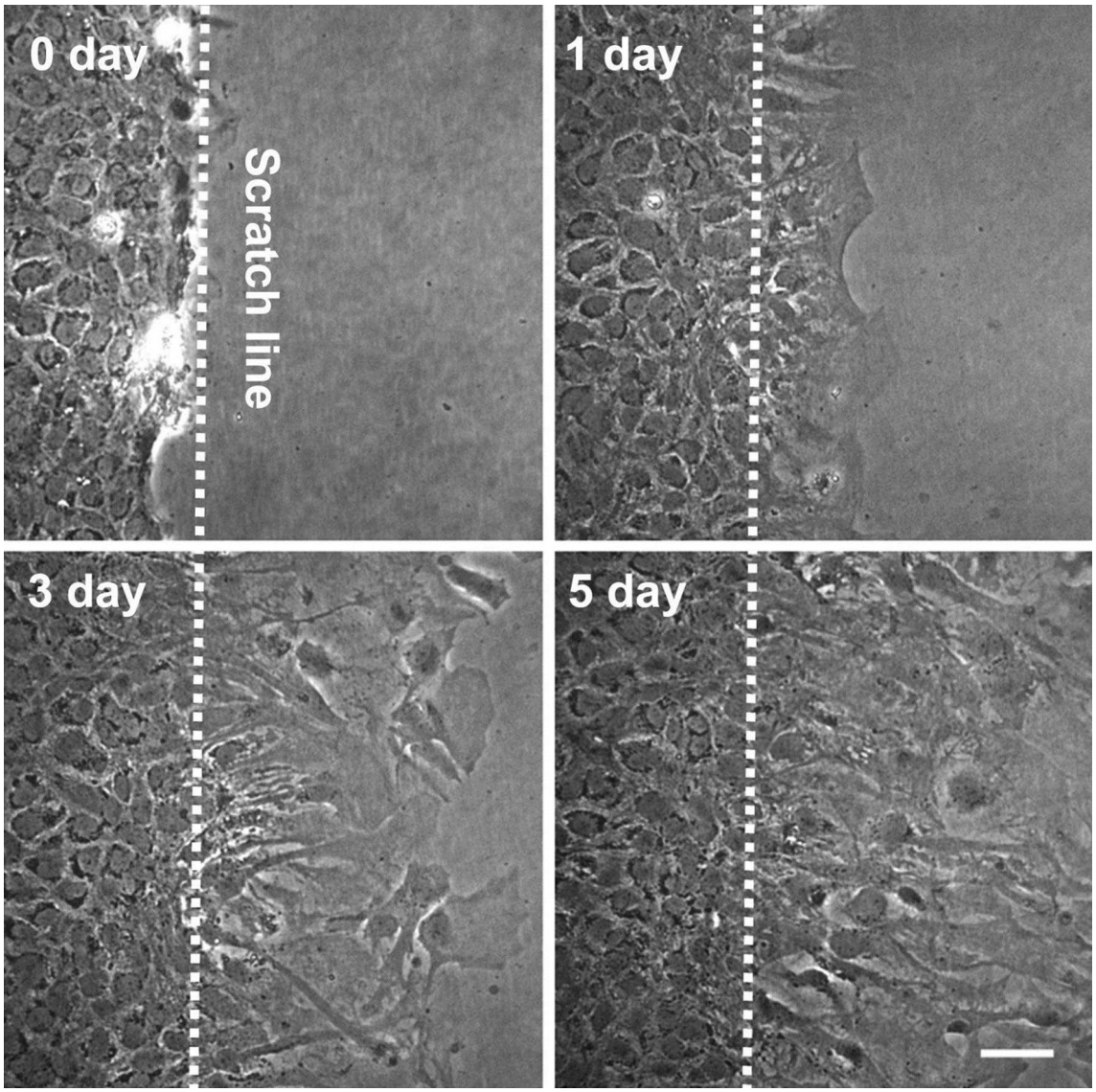

Fig. 2 Cultures after scratch injury under phase contrast microscopy. Astrocytes on the edge of scratch start to send pale and flat cytoplasmic processes toward the denuded area at day 1 after injury. The elongated cytoplasmic processes are clear to be observed. At day 3, cell migration and proliferation are more obvious. At day 5, the wound has closed. *Scale bar* represents 25 μm

attachment at the rear, both of which require the change of cell–cell/cell–ECM adhesion properties. Adhesion involves the binding of cell adhesion molecules (CAMs) located on cell surface with other cells or ECM to help cells sticking to each other and to their surroundings. Most of the CAMs belong to the five protein families including immunoglobulin (Ig) superfamily, integrins, syndercans, cadherins, and selectins. Most of these CAMs are calcium-dependent except Ig superfamily members [66], and each CAM has a different function via recognition of different ligands. Thus, defects in CAM expression would contribute to defects in cell adhesion and migration.

ECM contains various adhesives that contribute to organization of matrix and help cells to attach to it. Some of these adhesives are fibrous proteins, glycosaminoglycans, proteoglycans, glycoproteins including fibronectin and integrins which are essential for cell migration [67]. Fibronectin is one of the best characterized extracellular glycoproteins that helps organize the matrix protein. Fibronectin is secreted by various cell types as soluble protein dimer. After binding to integrins, fibronectin is converted into larger insoluble fibrils through a complex cell-mediated process [68]. The insoluble fibronectin forms a major component in ECM and Cell–ECM adhesion, which is usually mediated by fibronectin and integrin binding.

Table 1 A summary of methodologies in cell migration study

	Methods/models/applications	Imaging techniques	References
In vitro	Scratch-wound assay		
	Single scratch introduced for fibroblast cell division study	Phase contrast/video microscopy	[45]
	Improved multi-scratch model for astrogliosis study	Phase contrast microscopy	[40]
	Chemotaxis assay		
	Dunn chemotaxis chamber	Phase contrast/video microscopy	[46]
	Boyden chamber	Phase contrast	[47]
		3D confocal microscopy	[48]
	Transwell® invasion assays	Phase contrast	[49]
	Beads applied in chemotaxis assay	Phase contrast	[50]
	HGF-induced cell scatter assay	Video microscopy	[51]
	High throughput technique monitoring cell migration		
	A micro-channel based assay	Phase contrast/video microscopy	[52]
	Functional screening detecting random cell migration assay	Live cell fluorescence microscopy	[53]
	Automated velocity mapping of migrating cell populations	Live cell fluorescence microscopy	[54]
	Border cell migration for live imaging and genetic analysis of collective cell movement	Live cell fluorescence microscopy	[55]
	Shear stress detecting under flow	Live cell fluorescence microscopy	[56]
	Neuronal growth cone motility and guidance	Live cell fluorescence microscopy	[57]
	Spheroid confrontation assay monitoring three-dimensional migration	Video microscopy	[58]
Ex vivo	Measuring invasion in an organotypic model	Phase contrast/video microscopy	[59]
	Chemotactic leukocyte migration in 3D environments	Video microscopy	[60]
In vivo	Using caenorhabditiselegans as a model system	Live cell fluorescence microscopy	[61]
	Assessment of development and chemotaxis in *Dictyosteliumdiscoideum* mutants	Video microscopy	[62]
	Drosophila hemolytic inflammatory cell migration in the zebrafish	Live cell fluorescence microscopy	[63]
	Experimental and spontaneous metastasis assays in mice	Two-photon/multi-photon microscopy	[64, 65]

Deposition of fibronectin creates an environment in favor to astroglial scar formation [69]. Fibronectin also has profound effects on wound healing, including the formation of proper substratum for cell migration and growth [68].

Integrins and syndecans are the two major classes of CAMs [70], with integrins being studied more extensively than syndecans. Integrins are regulated receptors and activated by inside-out signaling to engage in a certain specific cell adhesion and could also modulate their own activation in response to mechanical forces [71, 72]. They serve as bidirectional mechano transducers connecting the ECM to the cytoskeleton. This occurs through the binding of Arg-Gly-Asp (RGD) tripeptides of integrins and syndecan-4 to the heparin-binding domain of other proteins. Integrins a5b1 and avb3 are fibronectin receptors and could change the integrin compositions of cell–matrix adhesions under development, angiogenesis, wound healing and cancer progression. Both receptors trigger signaling pathways, including the activated RhoGTPases such as RhoA and Rac1 [60].

During CNS disturbances, integrin network rearrangements are common and its signaling could induce reactive phenotypes such as proliferation and migration in astrocytes [73]. The expression and assembly of integrins are immediately altered during astrocyte migration, such as in the case of cerebral ischemia, a decrease in integrin expression concomitant with astrocytic end-feet withdrawn from blood brain barrier, thus leading to an increase in vascular permeability [73, 74]. Furthermore, conditional deletion of integrin β1 in astrocytes would elicit glial migration [74]. In addition to their role in forming structural connections during quiescent stage, integrins also exhibit transmembrane receptor activity under activation and mediate Cdc42-regulated cell polarity via PKCζ, which initiates astrocyte migration [75]. Most recently, hyaluronan, the major component of ECM in brain and its receptor—CD44 adhesion protein was demonstrated to drive morphological changes of astrocytes via Rac1 Signalling [76]. Although it was shown previously that elevated CD44 in reactive astrocytes contribute to the change of astrocyte morphology [77], it was elucidated for the first time that regulation of Rac1 activity is responsible for this process. Moreover, it is very likely the induced Rac1 activity could enhance astrocyte migration and promote tumor progression [78, 79]. Apparently, CAMs and ECM components involved

in astrocyte migration still lack thorough studies and more works are needed before we can uncover relevant mechanisms involved in astrocytes migration.

Disruption of Contact Inhibition

Contact inhibition is a natural process that arrests the growth and migration of cells when they come into contact with each other. It regulates the development of organs and controls the responses of specialized tissues to injury [80]. It also exists in primary cultures. Contact inhibition between astrocytes limits their locomotion, process extension and migration, and consequently establishes a territory that excludes other cells. However, these astrocytes still communicate via gap junctions to make a functional syncytium, in certain cases, they create microdomains of isolated structural and functional units [81].

Contact inhibition establishes among astrocytes in the adherent junction with two key CAM molecules, cadherin and β-catenin. They belong to a family of transmembrane proteins that play a critical role in calcium-dependent cell–cell adhesion. The extracellular domains of cadherin form physical interaction among adjacent cells and their intracellular domains assemble with α/β-catenin to interact with the cytoskeletons [67, 82]. β-Catenin exerts dual functions of regulating the coordination of cell–cell adhesion and gene transcription. The cadherin cell adhesion multiprotein complex not only serves as a physically stable connection to chain up astrocytes, but also arrests the β-catenin on the plasma membrane from entering the nucleus so that genes mediating cell proliferation and differentiation could not be transcribed [83]. β-Catenin is usually stabilized on the plasma membrane and rarely translocated into the nucleus in adulthood unless adhesion complexes were disrupted under injury [84]. Disruption of contact inhibition rapidly releases β-catenin from the plasma membrane, allowing its entry into the cytoplasm and nucleus [85]. Injury initiates the canonical β-catenin/Wnt pathway in which Cdc42 is induced to mediate the activation of Par6-PKCζ and up-regulate β-catenin signaling components such as Wnt and Fzd-1, thus initiating β-catenin signaling pathway to inhibit glycogen synthase kinase 3β (GSK-3β). GSK-3β has recently been studied for its involvements in energy metabolism, neuronal cell development, body pattern formation and a number of diseases including cancer and bipolar disorder [86]. GSK-3β has been shown to phosphorylate β-catenin, thus targeting it for degradation. Inhibiting GSK-3β prevents β-catenin degradation and results in the accumulation of β-catenin in the nucleus to initiate gene transcription for migration, proliferation and differentiation of reactive astrocytes [85].

Polarity Formation in Astrocytes

Cells polarize in a number of ways to serve various purposes. The establishment and maintenance of cell polarity requires extracellular cues, membrane receptors, intracellular polarity complexes and related signaling pathways to work together to form a complex and comprehensive network. Plasma membrane and cytoplasm establish and maintain functionally specialized domains through complex mechanisms leading to cell polarization. These domains with different spatial arrangement and protein composition facilitate cellular processes such as differentiation, membrane growth and directional cell migration. Cells undergoing asymmetric divisions, resulting in two daughter cells with different fates and purposes would develop a marked, stable apical and basal polarity [87]. Cell types capable of migration must establish the front–rear polarity, e.g., the molecular and functional differences between the cell front and rear [88]. The front leading edge is defined by cell membrane flat ruffling—lamellipodium or thin protrusions—filopodia. Actin component in these structures polymerizes in the direction of migration and allows cells to extend the leading edge of the cell and to attach to the surface. The rear of the cell is loaded with bundles of actin microfilaments known as stress fibers. They contract and pull the trailing edge forward to keep up with the rest of the cell. Without this front–rear polarity, cells would be unable to coordinate directed migration.

Polarity is established by asymmetrically activating specific receptors belonging to the superfamily of G protein-coupled receptors (GPCRs) [89]. These superfamilies are usually distributed homogeneously on the plasma membrane [90]. Previous studies demonstrated that one GPCR receptor EBI2 (Epstein-Barr virus-induced gene 2) is highly expressed in immune cells. It could be activated by oxysterols and plays an important role in T cell-dependent antibody response and B cell migration [91]. Recent research has found that astrocyte migration also involves the activation of EBI2 which stimulate Ca^{2+} signaling and ERK phosphorylation [91]. The EBI2 induced astrocytes migration has become the first evidence of this receptor playing additional roles beyond the immune system [91, 92].

In the establishment of cell polarity, there are widely conserved signaling pathways including kinases, phosphoinositides and GTPases. A good example in astrocyte is the PLC-PKCα signaling pathway being activated by the asymmetrically recruited and activated heterotrimeric G-proteins to create cell polarity formation during migration [75]. These events would also lead to the local second messengers (DAG and IP3) accumulation and protein phosphorylation [90]. Orexin-A is an important neuropeptide involved in the regulation of feeding, arousal, energy consumption,

and reward seeking in the body. It has been shown that orexin-A stimulates the phosphorylation of ERK1/2 and then facilitates the migration of astrocytes via PLC-PKCα signaling pathway [93]. Through the interactions with phosphatidylinositol lipids, G-proteins and protein kinase C, it recruits various proteins and target them to appropriate cellular compartments, thus enabling them to interact with other components of the signal transduction pathways.

Another group of molecules, Rho-family small GTPases (RhoA, Rac and Cdc42) [94] are also known to play key roles in astrocyte polarity formation during migration. Cdc42 is known to be the center of polarity, with its activity controlled precisely both temporally and spatially by various extracellular cues such as soluble agonists, interactions between cell–matrix and cell–cell, as well as intracellular signals generated by the cell-cycle machinery. Cdc42 is also capable of controlling cell protrusion at the leading edge, nuclear positioning, microtubule organization, and actin polymerization [95] via coordinating multiple signal transduction pathways [96]. A recent study has shown that stimulation of astrocytes by neuronal surface protein Thy-1 precludes cell migration. Prolonged Thy-1-receptor interaction inhibits RhoA activation while activating FAK, PI3K and Rac1 [97]. With limiting knowledge in cell polarity in astrocyte migration, more research is necessary to understand the conservation and specificity of cell polarity in migration of reactive astrocytes and their influence on CNS repair.

Cytoskeleton Mobilization in Astrocyte Migration

Cytoskeleton is composed of intermediate filaments (IFs), actin filaments and microtubules. Actin cytoskeleton is the basic engine of cell movement, which is regulated by small GTPase such as Rho, Rac and Cdc42. Microtubules are important in cell polarity maintenance, interphase chromosome movement and cellular motility in general [98]. IFs, however, are the most puzzling cytoskeleton component whose composition specifically depends on cell types, developmental stages, and even particular functions carried out by a cell, such as wound healing. Astrocytes undergo reactivation with remarkable spatial changes in shape, structure, and function upon the severity of the injury. Primary cultures of astrocytes and reactive astrocytes in vivo both produce three IF proteins including GFAP, vimentin and nestin. Astrocytes lacking IFs change their motile behavior, confirming that IFs are an integral part of the astrocytic motile machinery, although the cellular events determining movement direction seems to be independent of IFs, which may indicate compensation by some other mechanisms [99]. In astrocytes, the down-regulation of astrocytic cellular speed and reduction in cellular processes in the absence of IFs indicate that IFs play a role in both process protrusion and cell locomotion, although whether some other parts of the cytoskeleton also cooperate with such processes remains elusive. Nevertheless, the impaired migration of IFs deficient astrocytes is at least partially responsible for the slowing down of post-traumatic glial scar formation and impaired wound healing process observed in GFAP−/−Vim−/−mice [99]. Modulating IFs production in astrocytes could ultimately contribute to the interference of astrocyte motility, such as during CNS injury.

Aquaporins in Astrocytes

Aquaporins (AQPs) are transmembrane proteins that allow transport of water molecules across plasma membrane, and have previously been found to have a strong impact on migration in a variety of cell types [100]. In astrocytes, the major water channel is AQP4 which is expressed throughout the CNS, particularly at the blood–brain and brain–cerebrospinal fluid barriers [101]. Compelling evidences of the involvement of AQP4 in astrocyte migration is discussed as follows. The M1 heterotetramer isoform of AQP4 is freely mobile in plasma membrane and diffuses rapidly into extending lamellipodial regions to support astrocyte migration [102]. Deficiency of AQP4 in astrocytes causes a slower cell migration following injury with or without chemotactic stimulation, leading to reduced scar formation via a mechanism involving AQP4—facilitated water flow in lamellipodia of migrating astrocytes [103, 104]. It has also been proposed that elevation of AQP4 expression in astrocytes under persistent fetal vasculature conditions contributes to the abnormally faster migration as compared to wild type astrocytes [105]. Although AQP4 was found to be a specific effector in astrocyte migration, only a few reports showed that AQP4 was also involved in human glioma and neural stem cell migration in the brain [106, 107]. Other AQPs associated in astrocyte migration however remain largely unknown. Nevertheless, in our previous study, we have found the expression of AQP5 in astrocyte. Under scratch injury, AQP5 was up-regulated and polarized to the migrating processes and plasma membrane of astrocytes in the leading edge of the scratch. The overexpressed AQP5 appears to facilitate astrocyte process elongation [43]. Therefore, modulation of the expression or function of AQP4 and AQP5 might provide implications in cell movement events.

Calcium in Astrocytes

Calcium ion, the simplest second messenger, regulates astrocyte motility in different ways. Spatiotemporal calcium gradients control directional cell movement [108]. Calcium and calmodulin are also simultaneously involved in different signaling pathways regulating cell migration of both astrocytes and glioblastoma multiforme [109–111]. A calcium level modulating protein, ryanodine receptor type 3, is important in controlling the motility of astrocytes [112]. Moreover, calcium dependent effect was observed in the promotion of astrocyte migration by orexin-A which was discussed earlier for its contribution to astrocyte polarity formation [93]. Furthermore, the regulation of calcium flow direction through a voltage-gated sodium channel $Na_v1.5$ leads to the modulation of injury-induced astrogliosis [113]. In addition, our recent study shows that calcium mobilization triggered under scratch injury switches on GFAP expression in astrocytes and promotes glia scar formation [42]. As more exciting discoveries are being made, a more systematic study is needed to fully elucidate the important roles of calcium in astrocyte migration.

Future Directions

With the emergence of compelling evidence, it is clear that migration of astrocytes under either physiological or pathological conditions is a very complex process. It involves various elements that range from adhesion molecules, contact inhibition, polarity, cytoskeleton, aquaporins, calcium and so forth. Although these elements interact with each other in controlling astrocyte migration, it is also noteworthy that they are also regulated by an extensive signaling network related to various astrocytic functions. Moreover, the effector mechanisms reviewed here and beyond on astrocyte migration may provide clues to what research direction should be driven. For example, why do injured astrocytes and glioma cells share many similar features [114]. Thus, migration in astrocyte still requires more research attention in order to delineate the molecular mechanisms which may provide fundamentals for the future development of clinical interventions for astrogliosis and glioma metastasis.

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