

Regulation of neurogenesis by extracellular matrix and integrins

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Deciphering the factors that regulate human neural stem cells will greatly aid in their use as models of development and as therapeutic agents. The complex interactions of cells with extracellular matrix (ECM) proteins probably contribute to proper central nervous system development mediating processes which regulate proliferation and differentiation of neural stem/progenitor cells. Many of these interactions involve transmembrane integrin receptors. Integrins cluster in specific cell-matrix adhesions to provide dynamic links between extracellular and intracellular environments by activation of numerous signal transduction pathways which may influence cell behaviour profoundly by influence on both gene expression and post-transcriptional signalling cascade. In this review we introduced and discussed a number of extracellular and intracellular factors engaged in the transduction of signals induced by cell adhesion to its environment, including matrix components, extracellular proteolytic enzymes, integrins and non-receptor tyrosine kinases.

Key words: cell microenvironment, focal adhesion kinase, integrin signaling, metalloproteinases, neural stem/progenitor cells

INTRODUCTION

The discovery of persistent neural stem cells in the adult brain has raised hope to develop new therapeutic strategies for neurodegenerative diseases (for review see Park et al. 2010) primarily because of their intrinsic ability to self-renew and differentiate into all types of neural cells, including neurons, astrocytes and oligodendrocytes (Gage 2000). Two main remedial cell-based strategies have evolved from our understanding of stem cell biology. The first one consists of grafting neural stem/progenitor cells to replace the dying cells; the second aims at recruiting endogenous stem cells or progenitors to the lesion sites (Emsley et al. 2005, Scheffler et al. 2006).

Any effective cell replacement therapy as well as efficient stimulation of endogenous neurogenesis would require the basic understanding of mechanisms governing stem cells proliferation and efficient differentiation into a particular neural phenotype. Therefore, research efforts focused on identifying factors that

regulate and control fate decision become crucial in the promotion and understanding of the molecular, biological and physiological characteristics of this potentially useful stem cell type depending on the specific culture conditions and stimuli used. Increasing evidence indicates on the importance of the expression and production of both adhesion molecules and extracellular matrix (ECM) components, which contribute to the formation and function of a unique environment that produces induction-regulating signals which may be instructive or permissive to neurogenesis-associated processes (Luckenbill-Edds 1997, Bianco et al. 2001, Zipori 2004).

External environmental signals must integrate with intrinsic molecular machinery to control the fate choices of cells. One way that cells gather information about the chemistry of the environment and the properties of neighboring cells is by engaging in specific, receptor-mediated interactions with extracellular matrix and cell surface constituents and stimulation of numerous signal transduction pathways. These associations influence cell behaviour profoundly by exerting an impact on both gene expression and post-transcriptional signalling cascade.

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EXTRACELLULAR MATRIX

Several data published in the last decade indicate that ECM play pivotal roles in regulating stem cell differentiation, migration and proliferation during embryonic development (Suzuki et al. 2003, Flaim et al. 2005, Kihara et al. 2006). Furthermore, it has been documented that migration of mouse cerebellar neural precursor cells *in vitro* and *in vivo* through the nostril migratory stream of adult mouse (Murase and Horvitz 2002) as well as proliferation of mouse neuroepithelial cells (Drago et al. 1991, Kearns et al. 2003) are influenced by the ECM.

Because of its heterogeneous nature, ECM has the potential to tailor unique responses that are composition-dependent (Yarwood and Woodgett 2001, Andressen et al. 2005, Mruthyunjaya et al. 2010). In agreement with this assumption remain data indicating that integrin receptors-mediated signalling events triggered by cell adhesion to laminin are quite different from those triggered by adhesion to fibronectin (Gu et al. 2002). For example, signals transduced from laminin-1 and fibronectin through $\alpha 6 \beta 1$ and $\alpha 5 \beta 1$ integrins, respectively, are likely to antagonistically regulate cell proliferation and differentiation – fibronectin suppresses differentiation to promote proliferation of myoblast, whereas laminin has the opposite effect (Von der Mark and Ocalan 1989). Studies in cell culture showed that different cell types may have their own favoured ECM for development, depending probably on the repertoire of specific receptors – integrins, expressed on their cell surface, which in turn may define the type of ECM ligand most potent for neurogenesis. Whereas results obtained in our laboratory point to the most important role of fibronectin in stimulation of proliferation of human umbilical cord blood-derived neural stem cells (HUCB-NSCs; Buzanska et al. 2009, Szymczak et al. 2010), as well as migration of embryonic neural progenitors (Tate et al. 2004), it has been proven that laminin is the most permissive substrate in proliferation and differentiation of embryonic stem cell lines and cortical neural progenitors (Andressen et al. 2005, Flanagan et al. 2006). In the light of recently published data it became obvious that laminin is involved in the oligodendrocyte recruitment from neural HUCB stem cells and their differentiation (Synecka et al. 2009). On the other hand Ali and coworkers (1998) pointed out that prominent role in the regulation of the cortical progenitor

cells development as well as modulation of astroglial cells proliferation in culture (Goetschy et al. 1987), plays collagen IV. This ECM component may also function as a regulator of neurogenesis in *Drosophila melanogaster* by modulating the relevant genes in the developing CNS (Monson et al. 1982).

There is increasing evidence for specific, direct binding of growth factors to ECM proteins, which are responsible for an important part of ECM function (Iyer et al. 2008). Both fibronectin and vitronectin bind hepatocyte growth factor (HGF) and form complexes of HGF and ECM receptors leading to enhanced cell migration (Rahman et al. 2005). Similarly, vascular endothelial growth factor (VEGF) binds to specific domain of fibronectin and tenascin-C, and these associations promote cell proliferation (Wijelath et al. 2006, Ishitsuka et al. 2009). In the case of FN-VEGF binding, the effect on proliferation requires the binding sites for integrins and VEGF to be in the same molecule, suggesting a requirement for juxtaposition of the two receptors. In some situations ECM proteins can synergize the growth factor in affecting neurogenesis associated processes (Alam et al. 2007).

The function of ECM in neurogenesis may be associated with particular patterns of proteolysis of extracellular matrix. The consequences of proteolytic cleavage are varied and complex and are thought to include both changes in the physical constraints of the pericellular environment as well as signalling through the liberation of normally sequestered molecules such as growth factors or exposure of latent bioactive fragments (Nagase and Woessner 1999, McCawley and Matrisian 2001, Schenk and Quaranta 2003). Thus, the state of the macromolecules within the ECM is of critical importance and proteolysis is a major factor leading to changes in the ECM. In this context enzymes that modify the extracellular matrix and modulate both the axonal guidance and cell adhesion molecules are of particular pertinency (Ethel and Ethel 2007). The matrix metalloproteinases (MMPs) are one of such group of proteases that are postulated to play important role in ECM remodeling required for many developmental processes.

METALLOPROTEINASES IN NEUROGENESIS-ASSOCIATED PROCESSES

The matrix metalloproteinases by processing of a variety of pericellular substrates including extracellu-

lar matrix proteins, cell surface receptors, cell adhesion molecules and growth factors (Fig. 1), initiate, modulate and terminate a wide range of important cellular functions and participate in numerous physiological and pathological processes (for review see Dzwonek et al. 2004, Yong 2005, Gasche et al. 2006). Although MMPs, in particular gelatinases - MMP-2 and MMP-9, have been investigated in the context of their detrimental role in brain ischemic injury, several studies suggest that they also beneficial for mediating neurogenic response of neural stem/progenitor cells. MMPs are expressed abundantly in neural stem cells isolated from human nervous system (Frolichsthal-Schoeller et al. 1999) and according to Mannello and others (2006) they have regulatory roles during the proliferation and differentiation of neural precursor cells in the embryonic development of the mouse brain. Particularly high expression levels of MMP-9 were detected in progenitor cells associated with the development of specific structures such as hypophysis, ganglion cell layer and retina, and in aggregates that would form highly vascular gray matter of the brain (Canete-Soler et al. 1995). Furthermore, Morris and coauthors (2006) reported that mRNA expression of both MMP-9 and/or MMP-2 in neural progenitor cells of the neurogenic subventricular zone increased several-fold after ischemic insult in adult rats. It was also noticed that dynamic evolution of MMPs activity matches the progression of post-ischemic proliferation and differentiation of progenitor cells in dentate gyrus of gerbil and primate brains (Lu et al. 2008, Wojcik et al. 2009). Thus, based on the published reports, it is tempting to speculate about the participation of these enzymes in ischemic injury repair, favouring probably the migration of precursor stem cells from neurogenic to injured sites to replenish lost cells. Consistent with this hypothesis, there remains emerging in vitro and in vivo data that indicates the involvement of MMPs in neurogenesis and particularly in neuroblast migration across tissue matrices (Tsukatani et al. 2003, Yong 2005, Lee et al. 2006, Jablonska et al. 2009). These findings are in general agreement with the already reported regulatory roles of MMPs during proliferation, differentiation and migration of neural precursor cells isolated from human and rodents central nervous system (Mitra et al. 2005, Mannello et al. 2006, Bovetti et al. 2007, Barkho et al. 2008). Much conclusion relating the potential role of MMPs in neurogenesis has arisen from studies in HUCB-NSCs culture performed

in our laboratory. It was observed that inhibition of endogenous MMPs activity of HUCB-NSCs significantly reduced both their proliferation and their toward neuronal lineage differentiation (Szymczak et al. 2010). Further support to stress the importance of MMPs in neurogenesis as compared with other proteinases stems from the failure of serine proteinase and furin inhibitors (Pefabloc and Dec-RVKR-CMK) to modulate this process.

Despite accumulating evidence concerning participation of MMPs in neurogenesis it is not possible at present to define precisely which of their pleiotropic functions are linked directly to this phenomenon. The most probable scenario and consistent with the established function of MMPs is the proteolytic remodeling of ECM and/or modulation of other guidance molecules needed for progenitor migration and process elongation (Nagase and Woessner 1999, Oh et al. 1999, Hoshina et al. 2007).

In addition, the proteolysis-mediated modifications of the physical interactions between cell and ECM proteins may uncover cryptic sites or liberate soluble fragments (Gianelli et al. 1997, Xu et al. 2001) that promote migration. Thus, the activity of enzymes secreted to the extracellular compartment in DG area may be associated with the formation of a unique environment needed for neural progenitor development and migration (Deryugina et al. 1997, Vaillant et al. 1999, 2003, Bianco et al. 2001, Tsukatani et al. 2003, Zipori 2004, Ayoub et al. 2005, Yong 2005, Lee et al. 2006, Bovetti et al. 2007). This is in accordance with the finding that expression of MMP-9 is related spatiotemporally to granule-cell migration during postnatal development of the cerebellum (Vaillant et al. 2003) and that MMP-2 contributes to the motility of astrocytes (Ogier et al. 2006) by MMP-mediated breakdown of ECM barriers impeding cell movement.

Complementary to their role in cell migration, MMPs could also promote neurite extension of newly integrated progenitor cells as suggested by recent findings involving MMP-2 and MMP-3 in dendro-axonal growth of cortical immature neurons by degradation of inhibitory substrates as chondroitin sulfate proteoglycans (Zuo et al. 1998, Gonthier et al. 2009, Ould-yahoui et al. 2009). Although MMPs *per se* would normally be predicted to promote neural progenitor development, MMP-mediated conversion of several trophic factors, to their biologically active forms, including these stored within ECM, may also produce

signals supporting neurogenesis (Caloff 1995, Lee et al. 2001, Bruno and Cuello 2006). Vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGFbeta) represent two such examples.

Metalloproteinases conventionally thought as extracellular proteases were also present in neuronal nuclei in the neurogenic area of dentate gyrus (Wojcik et al. 2009). Our data are consistent with recent findings showing gelatinolytic activity in the neuronal nuclei of ischemic brain as well as in the nuclei of cultured astrocytes (Sbai et al. 2010, Yang et al. 2010). Such localization most likely implies that metalloproteinase activity may represent a general mechanism by which neural stem/progenitor cells adjust their gene expression program involved in cell cycle progression. However, there is a paucity of information about the effects of MMPs on the transcriptional factors that function in the differentiation. Hence, an understanding of this response would help to establish the intrinsic potential of the adult brain, and to reveal how we might use this mechanism for tissue restoration. However, it would need to be confirmed by further investigation.

The activity of metalloproteinases is controlled by the endogenous four tissue inhibitors – TIMPs 1-4. TIMPs exert a dual regulation of MMP activity by forming stable inhibitory complexes with the active site of MMPs (for example TIMP-1 forms an inhibitor complex with proMMP-9) and also by forming an activator complex which binds and activates MMP-2

(Morgunova et al. 1999). During neurogenesis, when progenitor cells generate the neurons and glia found in the mature CNS, altered cell-cell and cell-ECM interactions induced by imbalance in production of MMP and multifaceted TIMP may have profound consequences. On the one hand overactivation of MMPs and intensive cleavage of their extracellular substrate trigger intracellular signalling that leads to changes in neural progenitors, whereas on the other the inhibition of MMPs present in neuronal nuclei may change the mechanism responsible for expression of genes involved in cell progression. Regarding the function of TIMP it is rather surprising that almost nothing is known about their effects on neurogenesis. Nevertheless, all four TIMPs were detected in neuroepithelial stem cells isolated from human central nervous system (Frolichsthal-Schoeller et al. 1999). The presence of TIMP-2 was demonstrated in neural progenitors migrating from subventricular zone (SVZ). It was also found that TIMP-1 and TIMP-2 bound to alpha3beta1 integrin and may affect directly cell growth and differentiation, independent on their function in MMP inhibition (Lim and Alvarez-Buylla 1999, Seo et al. 2003). Further studies are needed to specify the participation of TIMPs in neurogenesis-associated processes.

INTEGRIN-MEDIATED SIGNAL TRANSDUCTION

ECM ligands provide outside-in signals for cells to sense their microenvironment and react to stimuli (Hynes 2002, Larsen et al. 2006). The proper response of extracellular signals is possible due to an array of integrin receptors on the cell surface and hence capable of triggering intracellular cascade of events instructive for maintenance of neural stem cells, cell proliferation, differentiation, migration and survival (Flanagan et al. 2006, Chen et al. 2007).

It is full agreement that integrins play roles during the development of several embryonic regions including central nervous system where beta 1 integrins influence the development of laminae and folia in the cerebral and cerebellar cortex (Georges-Labousse et al. 1998, Graus-Porta et al. 2001). Almost all the human neural stem/progenitor cells express the beta1 integrin subunit family of integrins. Thus, it is postulated that these integrin family controls various nervous system cell function, including cell migration (Anton et al. 1999, Tate et al. 2004). This is in concert with the finding that inhibition

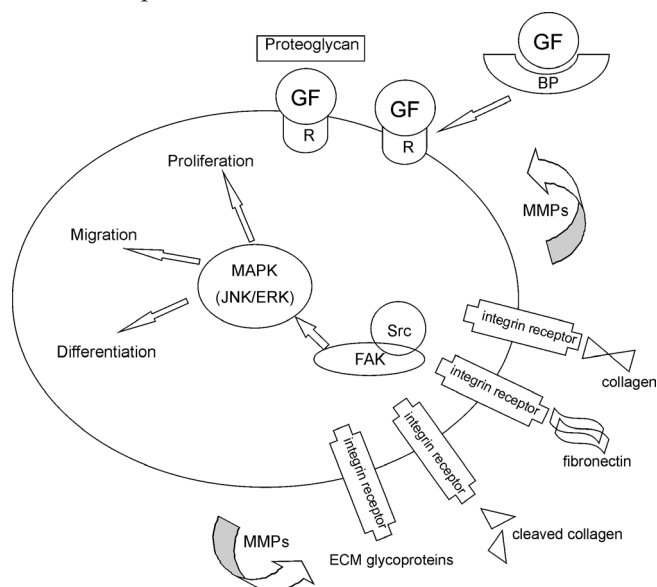


Fig.1. Matrix metalloproteinases regulate migration, proliferation, and differentiation of stem/progenitor cells.

of $\alpha 5 \beta 1$ expression in SVZ impairs neuronal migration (Marchetti et al. 2009). Several findings indicate, that distinct integrins may participate in the development of neural progenitors. This event is probably dependent on the type of specific ligand.

In addition to activating their own complement of signalling molecules, integrins have another major role – functional modulation of receptor tyrosine kinases. Integrin signalling and its close cooperation with growth factors-coupled pathway has been linked to the regulation of both survival and apoptosis in a variety of different cell types (Yamada and Even-Ram 2002), probably including also progenitors. In particular, high degree of functional interdependence was found between ECM and EGFR activated pathways. This kind of overlapping signal transduction is thought to support or enhance a number of ECM- and receptor tyrosine kinases-controlled cell functions, including proliferation, migration and survival. For example EGF regulates integrin-mediated cell migration that depends entirely on co-presentation with ECM components (Li et al. 2001, Kuwada and Lee 2000).

In contrast with the great progress made in recent years identifying various integrin complexes and their ligand specificity, little is known about the molecular mechanism by which integrins transmit information across the plasma membrane. Although they are presumably responsible for triggering the subsequent events leading to alterations in neurogenesis-associated processes – proliferation, migration and differentiation of progenitors, the immediate intracellular biochemical pathways induced by integrin/ECM ligand interactions are poorly understood.

Cell attachment to the ECM proteins generates integrin-mediated intracellular signal which leads to specific tyrosine phosphorylation cascade of a limited number of protein substrates, and these participate in regulation of cytoskeletal organization and gene expression presumably necessary for synthesis of specific molecules which may underlay the phenomenon of neurogenesis. This pathway involves a non-receptor tyrosine kinase called focal adhesion kinase (FAK), a key component responsible for the flow of information from ECM to the cell interior (Astier et al. 1997, Schlaepfer and Hunter 1998, Lim et al. 2004). Therefore, it is not surprised that numerous studies have demonstrated its regulatory role in cell cycle progression (Zhao et al. 1998, Oktay et al. 1999). Phosphorylated FAK may interact directly with downstream mole-

cules, and several of these can perhaps provide a pathway by which ECM may regulate cell viability (Illic et al. 1997, Giancotti and Ruoslahti 1999, Igishi et al. 1999). The results of several studies examining the levels of FAK expression and phosphorylation in a developmental context suggest a role for FAK in signalling events during early embryogenesis. FAK-deficient embryos show phenotypic defects in the late stages of gastrulation. It suggested a general defects in the migration of mesodermal cells, similar to that observed by fibronectin and $\alpha 5$ integrin deficient embryos (Goh et al. 1997). These observations remain in general agreement with in vitro and in vivo experiments showing FAK involvement in cell migration (Furuta et al. 1995, Illic et al. 1995), although there is still no consensus as to exact mechanism of its action in the regulation of this process. Reported correlation between elevated FAK expression and cell proliferation may be related to the formation of a new adhesion in the proliferating cells rather than to direct action of this kinase on cell proliferation.

The postulated influence of FAK on proliferation and differentiation of neural stem/progenitor cells is probably due to the activation of mitogen-activated protein (MAP) kinase pathway and phosphatidylinositol 3 kinase (PI3K) pathway (Campos et al. 2004, Tate et al. 2004). Inhibitors of these kinases show that both pathways synergistically activate survival signals in the embryonic stem cell-derived early neural stem progenitor cells (Ishii et al. 2010).

The MAP kinase including the extracellular signal-related protein kinases (ERKs), and the stress-activated kinases, c-Jun NH2 terminal kinases (JNK) and p38 MAP kinase, regulate neural cell proliferation and differentiation programs (Schaeffer and Weber 1999, Song et al. 2002, Weston et al. 2002). Both PI3K and ERK signalling play important roles in neurogenesis as demonstrated in neural progenitor cells dissociated from rat cortical neuroepithelium (Li et al. 2001) and in cerebral cortical cultures (Jin et al. 2005). Inhibition of these enzymes suppresses DNA synthesis in progenitor cells (Li et al. 2001). In agreement with these, inhibition of protein tyrosine phosphatases restored both Akt and ERK activities and enhances proliferation of progenitor cells in the adult SVZ (Matsumoto et al. 2006) and hippocampal subgranular zone (Shioda et al. 2008).

It is worth to point out that different signalling mechanisms have been described for distinct ECM proteins involving receptors of the integrin type (Fig. 2). For

example there are published data showing that ERK kinase plays a major role in mediating laminin-2 responses (Dowgiert et al. 2003), while Gu and coauthors (2002) suggests that signals from laminin-10 are PI3-kinase/Akt mediated. Conflicting reports of the role of signalling molecules in proliferation may be explained by the notion of cross-talk between the Ras-Raf-MEK-ERK and PI3K/Akt pathways demonstrated in several systems (Moelling et al. 2002). It has been hypothesized that cross-talk may be regulated by ligand type or concentration, cellular background or stage of differentiation.

In contrast to the above data suggesting the possible involvement of FAK in transmitting signals that regulate the development of stem progenitor cells, it seems rather surprising that nothing is known about the effect of closely related to the FAK proline-rich tyrosine kinase 2 (Pyk2) (Avraham et al. 1995). Pyk2 may also, similarly to FAK, interact with integrins and activate transduction pathway involving PI3 kinase (Chen et al. 1996). However, the most interesting is its ability to shuttle between the cell nucleus and cytoplasm (Aoto et al. 2002) and influence transcriptional activity. These properties may imply participation of Pyk2-coupled pathway in neurogenesis. Our preliminary study show increased Pyk2 tyrosine phosphorylation which coincides with ischemia-induced proliferation and differentiation of neural progenitor cells in the neurogenic dentate gyrus in gerbils (Ziemka-Nalecz et al. 2010). However, further studies are required to elu-

citate the engagement of Pyk2 in neurogenesis-associated processes. Continuing research along this line may provide better understanding of the complex role of the described above non-receptor tyrosine kinases.

SUMMARY

Collectively, the data present in this mini-review elucidate ECM-connected signalling events, which are different aspects of regulation of neurogenesis. It also addresses its significance and highlights the complexity of the cellular response to the cell-ECM interactions. However, it should be remembered that neuronal stem/progenitor cells development may be controlled by cooperative actions of many factors

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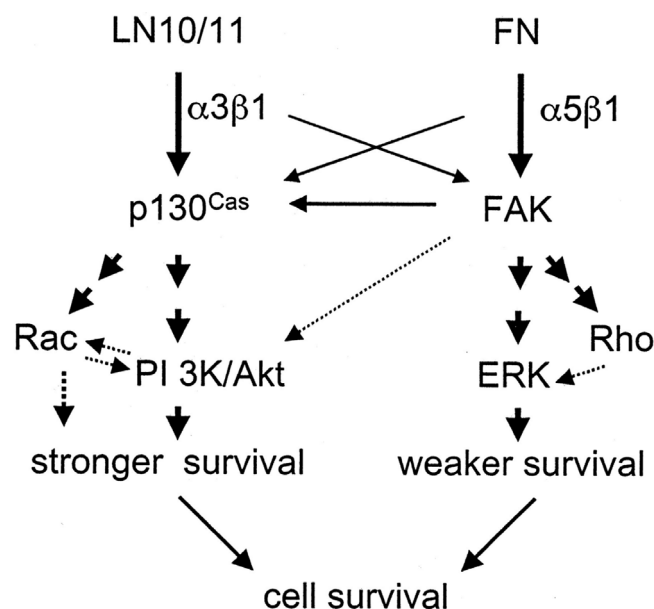


Fig 2. Extracellular signalling pathway induced by different ECM proteins (laminin and fibronectin).

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