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Review

The uPA/uPAR system in astrocytic wound healing

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From the Contents

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Abstract

The repair of injured tissue is a highly complex process that involves cell proliferation, differentiation, and migration. Cell migration requires the dismantling of intercellular contacts in the injured zone and their subsequent reconstitution in the wounded area. Urokinase-type plasminogen activator (uPA) is a serine proteinase found in multiple cell types including endothelial cells, smooth muscle cells, monocytes, and macrophages. A substantial body of experimental evidence with different cell types outside the central nervous system indicates that the binding of uPA to its receptor (uPAR) on the cell surface prompts cell migration by inducing plasmin-mediated degradation of the extracellular matrix. In contrast, although uPA and uPAR are abundantly found in astrocytes and uPA binding to uPAR triggers astrocytic activation, it is unknown if uPA also plays a role in astrocytic migration. Neuronal cadherin is a member of cell adhesion proteins pivotal for the formation of cell-cell contacts between astrocytes. More specifically, while the extracellular domain of neuronal cadherin interacts with the extracellular domain of neuronal cadherin in neighboring cells, its intracellular domain binds to β-catenin, which in turn links the complex to the actin cytoskeleton. Glycogen synthase kinase 3β is a serine-threonine kinase that prevents the cytoplasmic accumulation of β-catenin by inducing its phosphorylation at Ser33, Ser37, and Ser41, thus activating a sequence of events that lead to its proteasomal degradation. The data discussed in this perspective indicate that astrocytes release uPA following a mechanical injury, and that binding of this uPA to uPAR on the cell membrane induces the detachment of β-catenin from the intracellular domain of neuronal cadherin by triggering its extracellular signal-regulated kinase 1/2-mediated phosphorylation at Tyr650. Remarkably, this is followed by the cytoplasmic accumulation of β-catenin because uPA-induced extracellular signal-regulated kinase 1/2 activation also phosphorylates lipoprotein receptor-related protein 6 at Ser1490, which in turn, by recruiting glycogen synthase kinase 3β to its intracellular domain abrogates its effect on β-catenin. The cytoplasmic accumulation of β-catenin is followed by its nuclear translocation, where it induces the expression of uPAR, which is required for the migration of astrocytes from the injured edge into the wounded area.

Key Words: astrocytes; lipoprotein receptor-related protein 6; plasmin; urokinase receptor; urokinase-type plasminogen activator; Wnt-β-catenin pathway; wound healing; β-catenin

Introduction

Tissue repair is a multifaceted process mediated by activation of signaling pathways in the immune, inflammatory, and coagulation systems (Gurtner et al., 2008). More specifically, injury-induced phenotypic and gene expression changes in cells of these systems trigger a series of events that allow them to proliferate, differentiate and migrate (Singer and Clark, 1999) through a sequence of steps that if are not tightly coordinated may lead to the development of malignancy and fibrosis (Gurtner et al., 2008).

Cell migration is pivotal for wound healing. Indeed, the repair of wounded epithelial monolayers (Poujade et al., 2007), corneal epithelium (Buck, 1979), skin (Vitorino et al., 2011), and astrocytes (Diaz et al., 2021) is contingent upon the induction of directional cell migration and subsequent reestablishment of intercellular adhesions. More specifically, cell migration during wound healing involves the disassembly of intercellular adhesion, the migration of cells into the wounded area, and the final reconstitution of previously damaged cell-cell contacts. Importantly, the fact that injured cells move at similar migration speeds, and that their trajectory exhibits minimal changes relative to their original position (Zhao et al., 2003), has been postulated to be a mechanism that allows them to reestablish their intercellular connections once they have migrated (Tanner et al., 2009).

The repair of the damaged central nervous system is a more complex process that besides cell migration also requires the abrogation of endogenous inhibitory signals and reestablishment of neural networks. Significantly, a growing body of experimental evidence has revealed that astrocytes have an extensive molecular repertoire that allows them to become the focal point of neurorepair, and that astrocytic activation and migration are pivotal events in the process that leads to the restoration of the damaged central nervous system (Sofroniew, 2009). In line with these observations, our experimental *in vitro* and *in vivo* works (Merino et al., 2016; Diaz et al., 2017, 2018, 2021) have shown that binding of the serine proteinase urokinase-type plasminogen activator (uPA) to its receptor (uPAR) triggers astrocytic activation and migration and that both events are crucial for synaptic repair (Diaz et al., 2018, 2020; Diaz and Yepes, 2018).

Data Source

A PubMed literature search of articles published in the period of January 1968–October 2021 was performed on urokinase-type plasminogen activator and astrocytic wound healing.

The uPA/uPAR System

UPA has a growth factor-like domain, homologous to the epidermal growth factor, that binds to uPAR; a kringle domain that interacts with plasminogen-activator inhibitor-1 [PAI-1; uPA's inhibitor (Lawrence et al., 1989)]; and a protease domain that harbors the amino acids His204, Asp255, and Ser356. During development, uPA is abundantly found in oligodendrocytes and neuronal extensions (Dent et al., 1993). In contrast, in the adult brain uPA is detected in a subgroup of glial cells, in synapses of neurons located in the II–III and V cortical layers (Diaz et al., 2020), and in the cell body of well-defined groups of neurons in the basal ganglia (Masos and Miskin, 1996).

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The receptor for uPA (uPAR) is assembled by three domains (D1, D2, and D3) that bind uPA and its amino-terminal factor (contains uPA's D1 and D2 domains but not D3 and thus lacks proteolytic activity) (Andreasen et al., 1997), that are anchored to the cell surface by a glycosylphosphatidylinositol tail. In contrast with early developmental stages when uPAR is found in a large number of neurites, in the mature brain this receptor is detected mostly in dendritic and axonal growth cones. The expression of uPAR is regulated by various cell signaling pathways, including the Ras-extracellular signal-regulated kinase-mitogen-activated protein kinase (Vial et al., 2003), hypoxia-inducible factor-1α (Krishnamachary et al., 2003), and nuclear factor κB (Wang et al., 2000). In this review, we discuss our finding that by activating the Wingless/Int1 (Wnt)-β-catenin pathway, uPA regulates the expression of uPAR on cerebral cortical astrocytes (Diaz et al., 2021).

Following its binding to uPAR on the cell surface, uPA cleaves the zymogen plasminogen into the protease plasmin, which in turn favors cell migration by triggering pericellular proteolysis (Smith and Marshall, 2010). However, besides catalyzing the generation of plasmin on the leading edge of migrating cells, uPAR also promotes cell migration and proliferation by activating cell signaling pathways like Ras-mitogen-activated protein kinase, Src, Tyr kinases focal adhesion kinase, and phosphatidylinositide 3-kinase (Vial et al., 2003). In agreement with these data, we found that uPA released by injured astrocytes prompts cell migration from the border of the injury into the wounded zone by activating the Wnt-β-catenin pathway.

Role of uPA/uPAR in injury and repair

A growing body of experimental evidence indicates that uPA and uPAR play a pivotal role in the repair of an injured tissue. Hence, the expression of uPAR increases after various forms of stress and injury (Romer et al., 1994; Floridon et al., 1999; Beschorner et al., 2000), and uPA has been found to prompt wound healing in various experimental paradigms (Carmeliet et al., 1997; Wysocki et al., 1999; Shen et al., 2012). However, independently of the differences in their design, a common theme that emerges from these reports is the fact that the role of uPA on wound healing requires plasmin generation. Our experimental *in vitro* and *in vivo* works (Merino et al., 2016; Diaz et al., 2017, 2018, 2021) have shown that a mechanical injury to a monolayer of astrocytes induces the release of uPA, and that binding of this uPA to uPAR not only triggers the detachment of intercellular adhesions between astrocytes located in the injured area but also activates a cell signaling pathway that triggers wound healing by promoting their migration into the wounded zone (Diaz et al., 2021). These sequences of events bear a striking resemblance to those that mediate the induction of an epithelial-mesenchymal transition-like response in cancer cells, which require uPAR-triggered detachment of intercellular adhesion and subsequent induction of cell migration (Krishnamachary et al., 2003). However, we found that this effect does not require plasmin generation, as was also observed in astrocytes deficient on plasminogen ($Plg^{-/-}$). In line with these findings, treatment with recombinant uPA, or with its amino-terminal factor (binds to uPAR but is devoid of proteolytic activity), but not with plasmin, promotes the healing of monolayers of astrocytes that have suffered a wound injury (Diaz et al., 2021). Interestingly, we also found that the migration of astrocytes from the wounded edge is enhanced in PAI-1 deficient ($PAI^{-/-}$) astrocytes, suggesting that as previously described by others (Kjoller, 2002), PAI-1 modulates cell adhesion and migration by a mechanism independent of its protease inhibitory role.

Effect of uPA on β-Catenin-N-Cadherin Interaction

Cadherins are transmembrane glycoproteins that establish cell-cell contacts by engaging in Ca^{2+}-dependent homotypic interactions (Geiger et al., 2001). Neuronal cadherin [N-cadherin (NCAD)] is a type I cadherin that in the developing central nervous system is abundantly found in most neurons and astrocytes (Mendez et al., 2010). In astrocytes, NCAD regulates the directionality of astrocytic migration (Dupin et al., 2009) and is crucial for the formation of cell-cell contacts (Shih and Yamada, 2012). β-Catenin is a member of the armadillo repeat protein superfamily that plays a central role in wound healing (Cheon et al., 2006). In astrocytes, most of β-catenin is bound to the intracellular domain of NCAD and the actin cytoskeleton, thus playing a structural role by stabilizing intercellular adhesions (Ozawa et al., 1989; Yamada et al., 2005). The strength of the interaction between β-catenin and the intracellular domain of NCAD is regulated by phosphorylation at different sites in β-catenin and NCAD. For example, phosphorylation of β-catenin at Tyr654 triggers its detachment from cadherin (Piedra et al., 2001), which then is degraded by the proteasome following its phosphorylation by glycogen synthase kinase 3β (GSK3β) at Ser33/Ser37/Thr41. Our studies show that uPA induces the phosphorylation of β-catenin at Tyr654 and that this is followed by its release from NCAD (**Figure 1**) (Diaz et al., 2021). Surprisingly, this is not followed by its proteasomal degradation, but instead by its cytoplasmic accumulation. These results suggest that besides triggering the detachment of β-catenin from NCAD, uPA is also inhibiting the pathway that promotes its degradation.

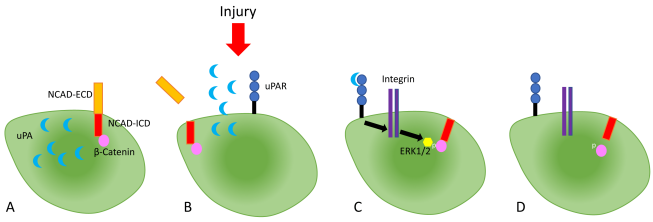

Figure 1 | Mechanism whereby urokinase-type plasminogen activator (uPA)/urokinase-type plasminogen activator receptor (uPAR) binding triggers the detachment of β-catenin from the intracellular domain of N-cadherin (NCAD-ICD).
(A, B) A mechanical injury to a monolayer of astrocytes induces the cleavage of the extracellular domain of NCAD (NCAD-ECD), the release of uPA, and the membrane recruitment of uPAR. (C) uPA/uPAR binding triggers the interaction of uPAR with integrins, which then activate extracellular signal-regulated kinase 1/2 (ERK1/2), thus leading to ERK1/2-mediated phosphorylation of β-catenin at Tyr654. (D) Once phosphorylated at Tyr654, β-catenin detaches from NCAD-ICD.

The Wingless/Int1-β-Catenin Pathway in Wound Healing

Wingless/Int1 (Wnt)-β-catenin pathway activation is a pivotal role in wound healing (Cheon et al., 2006; Bastakoty and Young, 2016; Zhang et al., 2018). When this pathway is inactive, GSK3β is bound to a cytoplasmic inhibitory complex assembled by axin and casein kinase Iα phosphorylates β-catenin at Ser33/Ser37/Thr41, prompting its ubiquitination and proteasomal degradation (Kikuchi et al., 2006). In contrast, the Wnt-β-catenin pathway is activated when a Wnt ligand (Wnt) binds on the cell membrane to Frizzled receptors and the extracellular domain of their transmembrane co-receptor, the low-density lipoprotein receptor-related protein 6 (LRP6). The formation of the Frizzled-Wnt-LRP6 complex leads to the phosphorylation of the intracellular domain of LRP6 at Ser1490 (pLRP6), which is required for Wnt-β-catenin pathway activation (Tamai et al., 2000, 2004). LRP6's phosphorylation triggers the recruitment of the axin inhibitory complex to the cytoplasmic tail of pLRP6, which in turn inactivates GSK3β, thus abrogating GSK3β-induced phosphorylation of β-catenin at Ser33/Ser37/Thr41. This sequence of events leads to the cytoplasmic accumulation and subsequent nuclear translocation of β-catenin, which then binds to the transcription factor T cell factor/lymphoid enhancer factor to activate Wnt-target gene expression (Kikuchi et al., 2006). Our studies show that uPA induces extracellular signal-regulated kinase 1/2-mediated phosphorylation of LRP6 at Ser1490 and that this effect leads to the cytoplasmic accumulation and subsequent nuclear translocation of β-catenin (**Figure 2**), via a mechanism that does not require plasmin generation, as it is also observed following treatment with uPA's amino-terminal factor (Diaz et al., 2021). Significantly, our results also revealed that following its nuclear translocation β-catenin triggers the expression of uPA's receptor (uPAR) and that either pharmacological inhibition of β-catenin or genetic deficiency of uPAR abrogates uPA-induced migration and healing of a monolayer of astrocytes that have suffered a mechanic injury.

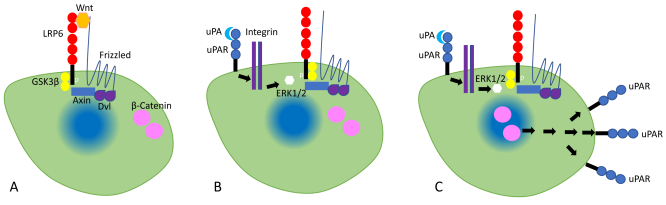

Figure 2 | Mechanism whereby urokinase-type plasminogen activator (uPA)/urokinase-type plasminogen activator receptor (uPAR) binding activates the Wnt-β-catenin pathway in astrocytes.
(A) Binding of Wnt ligands to Frizzled receptors and lipoprotein receptor-related protein 6 (LRP6) on the astrocytic membrane triggers the phosphorylation of the intracellular domain of LRP6 at Ser1490, which in turn leads to Dishevelled (Dvl)-mediated recruitment of the axin inhibitory complex, thus blocking glycogen synthase kinase 3β (GSK3β)-induced proteasomal degradation of β-catenin. (B) Binding of uPA to uPAR on the astrocytic membrane prompts integrin-mediated activation of extracellular signal-regulated kinase 1/2 (ERK1/2), which in turn phosphorylates LRP6 at Ser1490, independently of Wnt ligands binding to LRP6 and Frizzled. As depicted in A, this also leads to inhibition of GSK3β-triggered proteasomal degradation of β-catenin. (C) Following its cytoplasmic accumulation, β-catenin is translocated to the nucleus where it induces the expression of uPAR, which then triggers the migration of astrocytes from the injured edge into the wounded area.

Summary

Our studies show that uPA released by injured astrocytes induces wound healing by a two-pronged mechanism. First, it triggers the detachment of β-catenin from intracellular domain of N-cadherin, and second, it activates the Wnt-β-catenin pathway by phosphorylating LRP6 at Ser1490. The first step prompts the release of β-catenin from intracellular domain of N-cadherin, thus enabling the detachment of cell-cell adhesions required for astrocytic migration. The second step renders GSK3β incapable of promoting the proteasomal degradation of β-catenin, thus prompting its accumulation in the cytoplasm and subsequent nuclear translocation, where it induces the expression of uPAR, which is required for the migration of astrocytes from the injured border into the wounded zone. These events do not require plasmin generation and are regulated by PAI-1. Future studies are required to determine the mechanisms that deter cell migration once the wounded area is fully occupied by astrocytes. This is a new role for uPA with significant translational implications for neurorepair.

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