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Minireview

Molecules and Cells

Ninjurin1: a Potential Adhesion Molecule and Its Role in Inflammation and Tissue Remodeling

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Nerve injury induced protein 1, Ninj1 (Ninjurin1) is a cell surface protein that is induced by nerve injury and promotes axonal growth in the peripheral nervous system. However, the function of Ninj1 in the vascular system and central nervous system (CNS) is incompletely understood. Here we review recent studies that have shed further light on the role and regulation of Ninj1 in vascular remodeling and inflammation. Increasing evidence suggests that Ninj1 mediates cell communication and enhances the entry, migration, and activity of leukocytes such as monocytes and macrophages in developmental processes and inflammatory responses. Moreover, our recent studies show that Ninj1 regulates close interaction between leukocytes and vascular endothelial cells in vascular remodeling and inflamed CNS. Additionally, Ninj1 enhances the apoptosis-inducing activity of leukocytes and is cleaved by MMPs, resulting in loss of adhesion during tissue remodeling. The collective data described here show that Ninj1 is required for the entry, adhesion, activation, and movement of leukocytes during tissue remodeling and might be a potential therapeutic target to regulate the adhesion and trafficking of leukocytes in inflammation and leukocyte-mediated diseases such as multiple sclerosis, diabetic retinopathy, and neuropathy.

INTRODUCTION

Cell adhesion molecules provide the basis for cell-cell interaction, trafficking, and immune surveillance and regulate the fundamental biological process of cell division, cell movement, and cell death (Alter et al., 2003). Thus, the adhesive interaction is also crucial for tissue regeneration in development, inflammatory responses, and wound healing. These adhesion molecules provide a recognition system between leukocytes (including monocytes, macrophages, and neutrophils), endothelial cells, and matrix molecules and affect the phenotype and function of leukocytes. In particular, interaction between endothelium and leukocytes initiates their recruitment at sites of injury, infection, and inflammation. For example, cell adhesion mediated by selectins, integrins, and ICAMs plays a central role in the function of the immune system by initially tethering leukocytes to the endothelium and then enabling their emigration from the vasculature as part of tissue specific homing and recruitment at sites of inflammation (Elphick et al., 2009; Piqueras et al., 2009; Yi et al., 2009). Therefore, dysregulation of these adhesion molecules and their signaling pathways can give rise to continued recruitment and persistent activation of leukocytes with unresolved inflammation. Consequently, this area has become an important focus in the design of anti-inflammatory agents. In this review, we have summarized the current knowledge of Ninj1, a potential adhesion molecule that is involved in inflammation and tissue remodeling, in terms of its structure, distributon, regulation, and function. The possible functions of Ninj1 are discussed, together with the idea that interference with Ninj1 may be a useful approach to the future management of inflammation and many diseases mediated by leukocytes.

Ninjurin1, a potential adhesion molecule

Ninjurin family proteins (Ninjurins) are two-pass membrane proteins induced by nerve injury, thus increasing cell adhesion and neuronal regeneration in Schwann cells and dorsal root ganglion neurons (Araki et al., 1996; 1997). In the mammalian genome, there are two types of Ninjurins, Ninj1 and Ninj2, which share conserved hydrophobic regions in their transmembrane domains but differ in adhesion motifs and expression patterns (Araki et al., 1997). In humans, the amino acid sequence of Ninj1 is approximately 50% identical to that of Ninj2 and the Ninjurins have no considerable homology to any other known proteins (Araki et al., 1997). Furthermore, the tissue distribution of Ninjurins shows significant difference. In addition to its expression of the injured peripheral nervous system, Ninj1 is ubiquitously expressed in all tissues with epithelial origin (Araki et al., 1996; 1997). Meanwhile, the expression of Ninj2 is restricted to adult bone marrow and embryonic thymus (Araki et al., 2000) as well as mature sensory and enteric neurons. Since Ninj1 is expressed predominantly in epithelial cells, it may be concerned with the organogenesis of various tissues such as neurogenesis as well as neuronal regeneration, similar to neural cell adhesion molecule (NCAM), or L1 (Araki et al., 1996; Jakovcevski et al., 2007; Kim et al., 2001; Schlosshauer et al.,

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1984).

The *Ninj1* gene contains an open reading frame of 152 amino acids that encodes a predicted 16 kDa polypeptide (Fig. 1A). Ninj1 has two hydrophobic transmembrane domains (amino acids 72 to 100, and 118 to 139) and one putative N-glycosylation site (Araki et al., 1996). In addition, the critical homophilic adhesion domain of Ninj1 is located at an 12-residue region between Pro^{26} and Asn^{37} in the extracellular NH_2-terminal (ENT) domain and consists of a tryptophan and a cluster of arginine residues (Araki et al., 1997). Neither this motif nor a combination of tryptophan/arginines have been reported as functional residues in previously described adhesion molecules (Yamada et al., 1991). Adhesion assays using blocking peptides containing the adhesion motif reveals that Ninj1 may participate in heterophilic interaction as well as homophilic interaction (Fig. 1B). This heterophilic adhesion serves to extend the number of interactions and functions mediated by Ninj1 in many pathological conditions. Interestingly, co-expression of MMP1 and NijA (a fly homolog of vertebrate Ninj1) in *Drosophila* leads to liberation of the ENT domain of NijA, which either induces cell detachment or act as a signaling molecule (Fig. 1C) (Zhang et al., 2006). The differential role of the intact adhesion molecule and its shedding form has been reported previously for many adhesion molecules such as vascular adhesion molecule-1 (VCAM-1) and soluble VCAM-1 (Hummel et al., 2001; Kallmann et al., 2000; Osborn et al., 1989).

Ninj1 has been reported to play a diverse role in pathological conditions and developmental processes (Lee et al., 2009; Fig. 2). When developmental remodeling or pathogenesis processes are activated, the physical condition (oxygen gradient, pH, etc) is changed and many inflammatory cytokines are secreted. These signals activate leukocytes (monocytes, macrophages, and neutrophils) leading to increased expression of Ninj1 on their cell surfaces. Ninj1-expressing leukocytes can strongly adhere to endothelial cells and/or other leukocytes via homophilic or heterophilic modes and enter the site of inflammation or targeted tissues. Especially, in the CNS, this enhanced entry may be an important step in the progression of diseases such as multiple sclerosis by penetrating the blood-brain barrier (BBB). Finally, recruited Ninj1-expressing leukocytes are involved in phagocytosis, inflammatory/immune responses, and tissue reorganization. However, when MMPs cleaves Ninj1, the released ENT domain may suppress leukocyte-leukocyte and leukocyte-endothelium interactions mediated by intact Ninj1, resulting in resolution of the immune response and/or inflammation. Therefore, the function of Ninj1 related to the adhesion and migration of Ninj1-expressing cells may be crucial for many pathological conditions. Moreover, a number of reports have shown that Ninj1 is associated with several diseases. For example, Ninj1 is up-regulated in Schwann cells and dorsal root ganglion neurons after spinal cord injury (Araki et al., 1996), infiltrated blood cells of leprosy patients (Cardoso et al., 2007), B cells of acute lymphoblastic leukemia (Chen et al., 2001), and multiple sclerosis (Ahn et al., 2009; Tajouri et al., 2007). Furthermore, it has been known that Ninj1 may be associated with carcinogenesis since it has been reported to induce the senescence program and may be involved in the regulation of cellular senescence in the liver during carcinogenesis (Toyama et al., 2004). Ninj1 is also expressed in hepatocellular carcinoma (HCC) patients with regenerating nodules and could be involved in the formation and progression of HCC with cirrhosis related to viral infection (Kim et al., 2001). Taken together, these findings indicate that Ninj1 is an important adhesion molecule and can be a potential therapeutic target in many diseases.

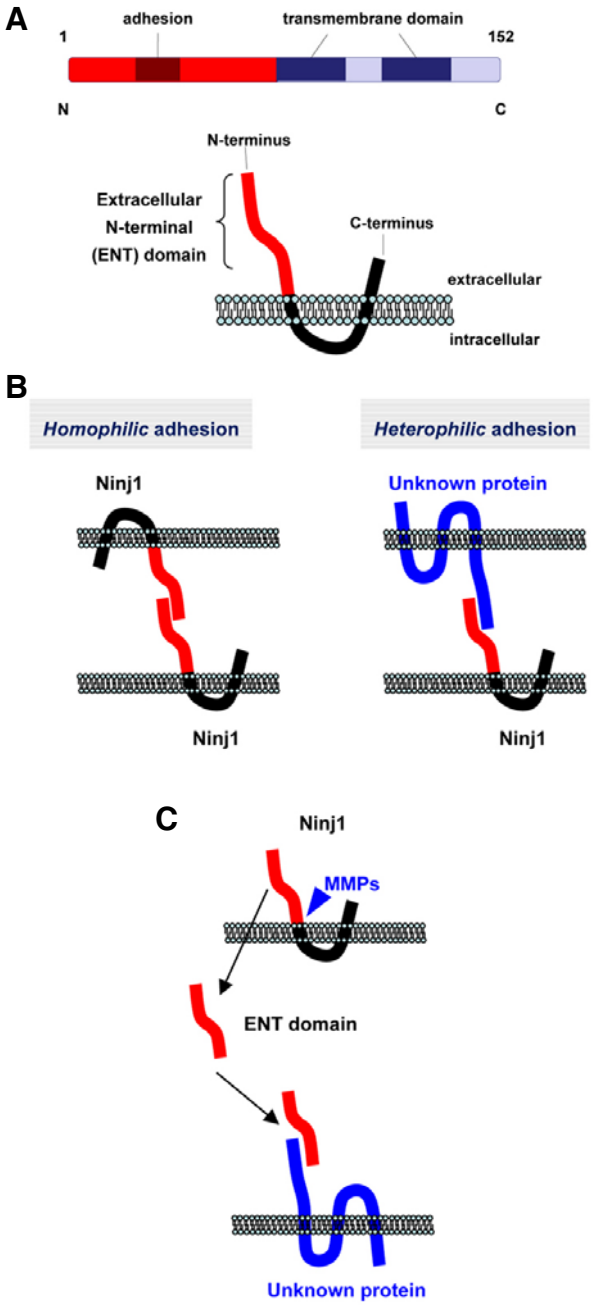

Fig. 1. The structure and adhesion functions of Ninj1. (A) Functional domain structure of Ninj1. Ninj1 contains one adhesion motif (dark red) and two transmembrane domains (blue) (upper). The predicted topology shows that Ninj1 has two extracellular domains (lower). The extracellular NH2-terminal (ENT) domain (red) contains adhesion motifs and the putative portion liberated by MMPs. (B) Two modes of adhesion mediated by Ninj1. Ninj1 is located at the cell surface and mediates either homophilic or heterophilic adhesion. (C) The ENT domain of Ninj1 is liberated by MMPs; the shed portion can interact with other cell surface molecules and might act as a signaling molecule (Zhang et al., 2006).

Regulation of inflammation by Ninj1

In general, inflammatory responses require close contact be-

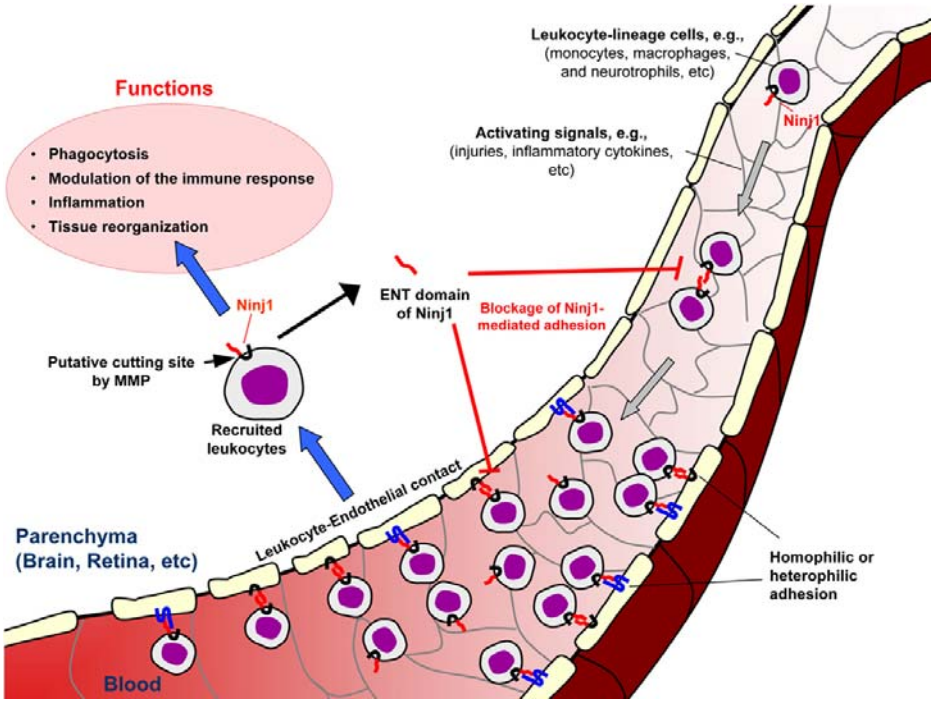

Fig. 2. Schematic diagram of potential functions of Ninj1 in inflammation and tissue remodeling. Various signals including injury and cytokines activate leukocytes (monocytes, macrophages, and neutrophils) leading to expression of Ninj1 on their surfaces. Ninj1-expressing leukocytes form aggregates and adhere to endothelial cells via either homophilic or heterophilic interactions. Subsequently, recruited Ninj1-expressing leukocytes may be involved in phagocytosis, immune response, inflammation, and tissue remodeling. However, when MMPs shed the extracellular NH2-terminal (ENT) domain of Ninj1, the liberated ENT domain may block the leukocyte-leukocyte and leukocyte-endothelium adhesion that is mediated by intact Ninj1, resulting in termination of the immune response and/or inflammation.

tween different populations of cells, including leukocytes and vascular endothelial cells. To date, there has been noteworthy progress in our understanding of this cell-cell interaction and several adhesion molecules have been actively studied. The adherence of leukocytes to the endothelium in the microcirculation is considered a critical initial event of the inflammatory process. Adhesion molecules mediate the migration and adhesion of leukocytes to the site of inflammation in a targeted fashion; for example, ALCAM-1 promotes the interaction of circulating leukocytes with vascular endothelial cells and their emigration into the tissue in inflammation (van Kempen et al., 2001). A number of adhesion molecules are known to be involved in leukocyte-endothelial cell interaction including ALCAM-1, ICAM-1, and VCAM-1 (Cayrol et al., 2008; Osborn et al., 1989). The wide diversity of the adhesion molecules is logical and provides delicate regulation of leukocyte recruitment, resulting in rapid and efficient elimination of the foreign pathogens. Therefore, identification of new adhesion molecules and inflammatory mediators will expand our understanding of the underlying molecular mechanisms of inflammation and provide the basis for novel therapeutic targets and strategies.

In addition to its involvement in cell-cell interaction following nerve-injuries, many studies suggested that Ninj1 plays a potential role in the inflammation process itself. Microarrays analyses have shown that NijA is up-regulated in *Drosophila* after septic wounding (De Gregorio et al., 2001). Moreover, the bacterial endotoxin, lipopolysaccharide (LPS) provokes a remarkable up-regulation of Ninj1 in *Drosophila* S2 cells (macrophage-like lineage), Raw264.7 cells, and BV2 cells (macrophage lineage) (De Gregorio et al., 2001; Lee et al., 2009). Following treatment of adult SD rats with LPS *in vivo*, a number of Ninj1-expressing leukocytes enter the vitreous and the border of the retina in a dose-dependent manner (Lee et al., 2009). Furthermore, microarray studies of multiple sclerosis revealed that Ninj1 is detected in inflamed brain, suggesting that Ninj1 is involved in the initiation or progression of multiple sclerosis (Tajouri et al., 2007). Multiple sclerosis is an autoimmune inflammatory disease of the CNS and the infiltration of leukocytes into the CNS is crucial for demyelination and axonal damage (McFarland et al., 2007). Recently, we reported that Ninj1 is expressed in leukocytes and some endothelial cells in multiple sclerosis and mediates leukocyte-endothelium interactions in inflamed CNS (Ahn et al., 2009). In normal CNS, Ninj1-expressing cells often appear in three major compartments of the brain in which cell-cell interaction mainly occurs: the meninges, the choroid plexus, and parenchymal perivascular spaces. When the CNS is inflamed, expression of Ninj1 is strongly increased in leukocytes and some vascular endothelial cells and many Ninj1-expressing leukocytes enter the CNS. Especially, these recruited leukocytes might act as antigen-presenting cells for T cells and produce cytotoxic cytokines, ultimately resulting in multiple sclerosis (McFarland et al., 2007). Collectively, these findings suggest that Ninj1 mediates the activation of leukocytes and their entry into the site of inflammation. Therefore, Ninj1 is a potential therapeutic target for several inflammatory diseases including multiple sclerosis. Furthermore, since the ENT domains of Ninj1 can interfere with the function of intact Ninj1, the ENT domain of Ninj1 may act as an endogenous negative regulator of the immune/inflammatory response (Fig. 2).

Regulation of tissue remodeling by Ninj1

Cell adhesion molecules play an important role in organogenesis and tissue regeneration after injury in multiple kinds of animal system, including embryonic tail (Chambon et al., 2002), interdigital epithelium (Guha et al., 2002; Montero et al., 2001), central nervous system (Ferrer et al., 1990; Jung et al., 2008), and hyaloids vascular system (HVS) (Saint-Geniez et al., 2004). The regulation of extracellular matrix and cell-cell interaction is important for proper tissue remodeling and homeostasis (Zhan et al., 2005). Furthermore, since many cells die by apoptosis or

are phagocytized during these processes, cell-cell interaction involving leukocytes is essential for tissue reorganization. Importantly, adhesion molecules confer delicate interaction between a leukocyte and its target cell, resulting in accurate and precise tissue remodeling. For example, many glycoproteins such as NCAM, N-cadherin, and L1 are involved in the regeneration of neurons (Miragall et al., 1989; Sunshine et al., 1987).

It has been reported that *Drosophila* NijA is expressed in tracheal cells and regulates tracheal remodeling by interaction with MMP1 (Zhang et al., 2006). During tracheal remodeling, the main trunk grows about 14-fold in length without cell division, therefore reorganization of cells is absolutely necessary (Gessner et al., 2000). NijA and MMP1 colocalize at the cell surface and MMP1 sheds the ENT domain of NijA. This induces loss of cell adhesion and enables reconstruction of the tracheal system (Zhang et al., 2006). The role of Ninj1 in tissue remodeling is not restricted to invertebrates: *Drosophila* tracheae are epithelial tubes and the underlying molecular mechanisms of *Drosophila* tracheal (respiratory) patterning and differentiation are similar to those of vasculogenesis and respiratory development in vertebrates (Affolter et al., 2003). Furthermore, since Ninj1 is widely expressed in epithelial cells in mammalian embryonic tissues, it is possible that Ninj1 plays a role in tissue remodeling in higher vertebrate. We recently showed that Ninj1 mediates rodent vascular remodeling via cell-cell interaction using the HVS (Lee et al., 2009), a transiently existing network of capillaries that regresses contemporaneously with the formation of retinal vasculature after birth (Saint-Geniez et al., 2004). During vascular remodeling, expression of Ninj1 in leukocytes promotes their adhesion and formation of clusters, contributing to leukocytes activation (Lee et al., 2009; Fig. 2). In general, activated leukocytes produce many molecules including basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β), and degrading enzymes (Sunderkotter et al., 1994). Especially, collagenase and TGF-β can change the composition and structure of the extracellular matrix during both angiogenesis and regression of vascular organs (Ambili et al., 1998). Therefore, adhesion of Ninj1-expressing leukocytes to the extracellular matrix of tissues might make vascular endothelial cells more accessible, leading to vascular morphogenesis. In HVS remodeling, Ninj1 increases Wnt7b expression in leukocytes and up-regulates the expression of Ang2 in pericytes (Lee et al., 2009). Since up-regulated Wnt7b increases the sensitivity of vascular endothelial cells to apoptosis and Ang2 reduces stability of endothelial cells (Lobov et al., 2005; Rao et al., 2007), Ninj1 expression eventually leads to apoptosis of the vascular endothelial cells. Collectively, our findings and other studies suggest that Ninj1 may not only facilitate the transport of leukocytes to the target site, where it participates in cell adhesion and provides more effective signaling to target cells, but also regulates the activity of leukocytes during tissue remodeling. Therefore, Ninj1 plays an important role in the proper development and function of a number of tissues such as tail or limb regression mediated by leukocytes.

CONCLUSION

It is generally accepted that leukocytes, including macrophages, perform an essential function in homeostasis, inflammation, and injury (Liang et al., 2007) and regulate the onset and progression of many diseases. For examples, these cells play an important role in cancer (Murdoch et al., 2008), rheumatoid arthritis (Pope, 2002), stroke (Liesz et al., 2009), and multiple sclerosis (McFarland et al., 2007). Therefore, regulating and preventing the adhesion and migration of leukocytes is considered as an effective therapeutic approach for treating these diseases (Luster et al., 2005). A number of studies have shown that monoclonal antibodies to selectins and integrin subunits can inhibit pathology in inflammatory disease models (Laudes et al., 2004). In many studies, administration of monoclonal antibodies abolished leukocyte infiltration, and antisense oligonucleotides have also proved to be effective (The et al., 2005). In conclusion, Ninj1 may be a potential mediator of tissue remodeling and inflammation by regulating the entry, adhesion, activation, and movement of leuokocytes. In addition, Ninj1 might be a novel therapeutic target for leukocytes-mediated pathophysiology such as inflammation and may also be beneficial in the opposite situation, in which wound healing or the host response to infections may be deficient.

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