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JNK is a novel regulator of intercellular adhesion

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c-Jun N-terminal Kinase (JNK) is a family of protein kinases, which are activated by stress stimuli such as inflammation, heat stress and osmotic stress, and regulate diverse cellular processes including proliferation, survival and apoptosis. In this review, we focus on a recently discovered function of JNK as a regulator of intercellular adhesion. We summarize the existing knowledge regarding the role of JNK during the formation of cell-cell junctions. The potential mechanisms and implications for processes requiring dynamic formation and dissolution of cell-cell junctions including wound healing, migration, cancer metastasis and stem cell differentiation are also discussed.

Introduction

c-Jun N-terminal Kinases (JNKs) are known as stress activated protein kinases (SAPK). They belong to the mitogen activated protein kinase (MAPK) superfamily, which also includes the ERKs and the p38 MAPKs.[1,2] JNKs were originally identified by their ability to phosphorylate c-Jun in response to stress induced by a variety of chemical or physical stimuli such as TNF-α,[3] heat shock,[4] osmotic stress,[5] or UV radiation.[6] It has been well-established that JNKs are activated by MAP2 kinases such as mitogen-activated protein kinase kinase (MKK) 4/7[7], and regulate apoptosis,[8,9] proliferation[10] and respond to stresses.[11]

Recently some studies have implied that JNK signaling may also be important during the formation of cell-cell junctions including adherens junctions (AJ), tight junctions (TJ), and gap junctions (GJ).[12–14] In addition, JNKs are involved in processes that require dynamic formation and dissolution of junctions, such as movement of epithelial sheets[15] during tissue development, cell migration during wound healing,[16] angiogenesis,[17] and tumor metastasis.[18]

This review will focus on studies that addressed the role of JNKs during the formation of cell-cell junctions and the processes requiring dynamic formation and dissolution of cell-cell junctions. The possible mechanisms and potential implications of JNK during epithelial development, wound healing, and cancer metastasis will be discussed as well.

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Overview of JNK Cascade and Function

Three genes are known to encode for JNK proteins. The *jnk1* and *jnk2* genes are expressed ubiquitously in all tissues, while *jnk3* is only expressed in brain, heart, and testis.[1] JNK proteins are encoded by alternative splicing of these three genes, *jnk1*, *jnk2* and *jnk3* to produce at least 10 isoforms.[19] There are two key alternative splicing sites: one is between subdomain IX and X of the C-terminal lobe of the protein; the second one occurs at the C-terminus of the protein. This causes 42 or 43 amino acids difference among JNK proteins.[20]

JNKs are typical serine/threonine kinases, comprising 11 protein kinase subdomains. The domains VII and VIII containing threonine and tyrosine residues form the activation loop. Complete activation of JNKs requires dual phosphorylation of these threonine and tyrosine residues within the loop. The protein kinase kinases, MKK4 and MKK7, are known to be the direct upstream activators of JNKs. MKK4 targets mainly tyrosine 185, whereas MKK7 phosphorylates preferably threonine 183. These protein kinase kinases are, in turn, phosphorylated and activated by upstream MAPKK kinases (MAPKKKs).[20,21]

MKK4 and MKK7 together with their respective scaffolding proteins activate different signaling pathways that mediate JNK activation in response to various stimuli.[22] Accordingly, JNK proteins play distinctive and sometimes opposing roles in cellular processes associated with proliferation, apoptosis, differentiation, or carcinogenesis. For example, in fibroblasts JNK1 promotes cell proliferation through activation of its downstream effector, c-Jun, whereas JNK2 inhibits cell proliferation by promoting c-Jun degradation.[10] JNKs are known to phosphorylate BH3-only subgroup of Bcl2-related proteins (Bim and Bmf) to induce Bax-dependent apoptosis,[23] but they can also phosphorylate pro-apoptotic Bcl-2 family BAD protein to inhibit apoptosis.[9] JNKs have been reported to be necessary for embryonic stem cells (ES) differentiation. $Jnk1^{-/-}$ $Jnk2^{-/-}$ ES cells exhibited major defects

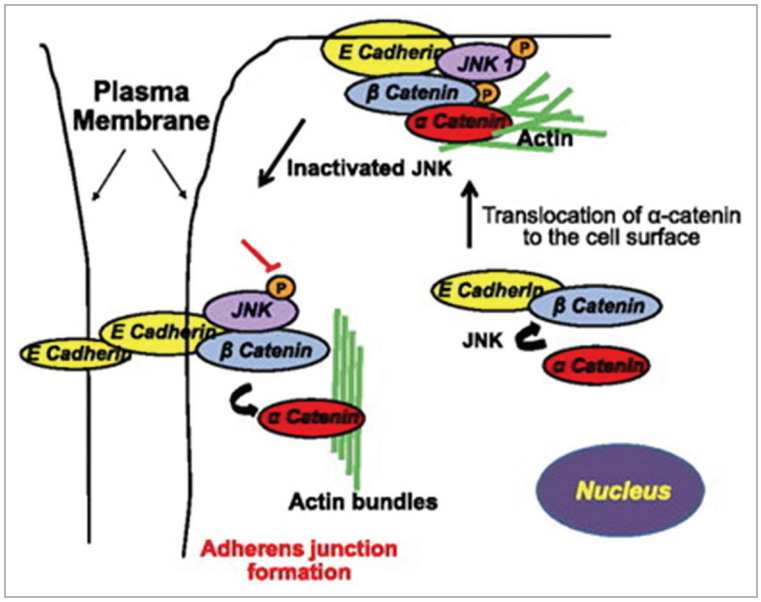

Figure 1. Schematic summarizing our recent findings. JNK binds to the adherens junction complex and phosphorylates β-catenin, preventing adherens junction formation. Upon inhibition of JNK kinase activity, β-catenin is dephosphorylated and adherens junctions are formed. Also α-catenin leaves the adherens junction complex and binds to actin, which is reorganized into parallel bundles underneath the adherens junction.[12,35] This figure was taken from Lee et al[35] with permission from the FASEB Journal.

in lineage-specific differentiation.[24] However, inhibition of JNK promotes differentiation of epidermal keratinocytes.[25] Distinctive stimuli affect JNK differently. JNKs promote leukemia oncogene Bcr-Abl-induced lymphoma in B cells[26] but suppress Ras-induced tumorigenesis in fibroblasts.[27] During different stage of tumorigenesis, JNK plays a dual role in the development of hepatocellular carcinoma.[28] Additionally, the duration of JNK activity matters. Ventura et al. reported that the early transient phase (< 1hr) of JNK activation protects cells from apoptosis, whereas the later and more sustained phase (1–6hr) of JNK activation mediates pro-apoptotic signaling.[29] These studies strongly indicate that the biological effects of JNK signaling depend on cellular context e.g., cell type, type of stimulus, and duration of JNK signaling.

Cell-Cell Junction Formation

Even though JNK regulates contradictory cellular responses such as proliferation, apoptosis, differentiation, or carcinogenesis, only recently it has emerged as a cell-cell junction regulator.

Adherens junctions

Cell-cell adhesion is crucial to many aspects of multi-cellular existence, including morphogenesis, tissue integrity and differentiation.[30] In epithelial cells AJ are formed by Ca^{2+}-dependent homotypic interactions between E-cadherins on the surface of opposing cells. The cytoplasmic domain of E-cadherin forms complexes with plaque proteins known as catenins, namely α- and β-catenin. The C-terminus of β-catenin interacts with E-cadherin whereas its N-terminal portion interacts with α-catenin. Monomeric α-catenin binds to the E-cadherin cytoplasmic domain via β-catenin, whereas dimeric α-catenin can bind and cross-link filamentous (F-) actin.[31] Phosphorylation of the cytoplasmic domain of E-cadherin results in enhanced cell adhesion,[32] whereas tyrosine phosphorylation of β-catenin has been implicated in AJ disassembly.[33] On the other hand, serine phosphorylated β-catenin can be incorporated in newly formed AJ but undergoes dephosphorylation as junctions mature.[34]

Recently, our group[12,35] and one other study[36] demonstrated that JNK plays an important role in AJ formation in epithelial cells. Our group reported that JNK phosphorylates β-catenin leading to AJ disassembly, whereas inhibiting JNK induces AJ formation and re-organization of actin into bundles right underneath the AJ.[12,35] Furthermore, blocking JNK resulted in AJ formation only in the presence of α-catenin, which dissociated from the E-cadherin/β-catenin complex and associated with the actin cytoskeleton[35] (**Fig. 1**). Interestingly, blocking JNK also resulted in AJ formation in two carcinoma cell lines, A431 and α-catenin ME180, revealing a previously unknown link between JNK and AJ.[35]

Similar observations were reported for intestinal epithelia where increased JNK phosphorylation correlated with disassembly of AJ and TJ. The JNK inhibitor SP600125 accelerated formation of AJ and TJ, while JNK activator anisomycin suppressed them. JNK1, not JNK2, was found to colocalize with junctions and knocking down JNK1 attenuated junction disassembly. Their findings also suggested JNK acts as a downstream target of actin-reorganizing Rho-dependent kinase (ROCK) and an upstream regulator of F-actin-membrane linker proteins of the ERM (ezrin-radixin-moesin) family.[36]

In addition, our group implicated JNK as a major regulator of substrate rigidity-mediated balance between cell-cell and cell-substrate adhesion (**Fig. 2**).[37] It is well known that stiffness of substrates mediates the cross talk between cell-substrate and cell-cell adhesion.[38] Under low

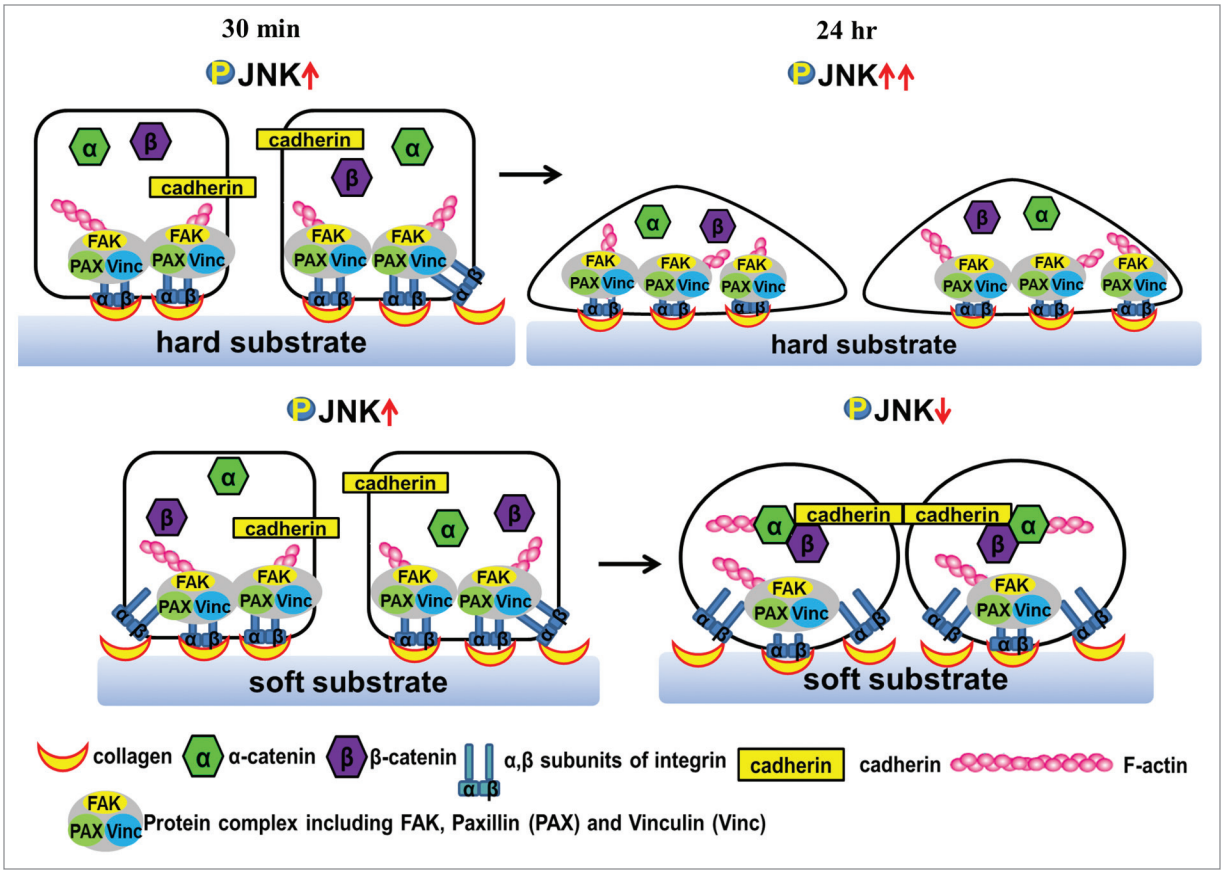

Figure 2. Schematic illustration of JNK regulating rigidity-dependent balance between focal adhesion (integrins) and cell-cell junction (cadherins).

Ca^{2+} concentration, epithelial cells prefer to stay as individual cells and adhere firmly on stiff substrate through integrin-mediated focal adhesion. On the other hand, on soft substrates, intercellular adhesion is favored and epithelial cells form colonies. The integrin-regulated cell-substrate adhesion is reduced and E-cadherin-mediated AJ formation is enhanced. Interestingly, we discovered that JNK, also a downstream target of integrin signaling, was phosphorylated on stiff and dephosphorylated on soft substrates. In addition, expression of constitutively active JNK induced AJ dissolution even on soft substrates, while JNK knockdown induced AJ formation even on hard substrates. In human epidermis, formation of AJ was severely compromised when JNK was activated either genetically or by use of stiff scaffolds. On the other hand, knocking down JNK induced strong AJ even in the basal layer of bioengineered epidermal tissues. Interestingly, the changes in AJ formation affected the architecture and differentiation state of epidermal tissue as well. Notably, similar results were observed in the epidermis of *jnk1*$^{-/-}$ or *jnk2*$^{-/-}$ mice and shRNA JNK1 and JNK2 bioengineered epidermis, supporting our hypothesis that JNK mediates the effects of substrate stiffness on AJ formation in 2D and 3D context, affecting the structure and differentiation status of epithelial tissues.

Tight junctions

The TJ is an intracellular junctional structure. TJ from neighboring cells not only mediate cell-cell adhesion but also serve as a fence to restrict the intramembrane diffusion of molecules from apical to basolateral membranes of polarized cells. More than 40 different proteins have been discovered in TJ complexes.[39,40] The most studied ones are claudins, occludin and Zonula occludens (ZO). The claudin family of transmembrane proteins has emerged as the most critical protein in charging selectivity.[41]

In epithelial cells, highly phosphorylated occludin proteins are selectively concentrated at TJ, whereas non-phosphorylated occludin mostly localizes in the cytoplasm.[42] Claudin phosphorylation regulates paracellular permeability - i.e., the flow of molecules in the intercellular space between the cells of epithelial tissues - depending on upstream kinase activity. For example, phosphorylation of claudin-1 and -4 by protein kinase C is required for TJ assembly in intestinal epithelial,[43] while phosphorylation by protein kinase A reduced incorporation of claudin-3 into TJ.[44] Both occludin[45] and claudins[46] are capable of binding to ZO-1, -2 and -3. As polarization of the epithelia proceeds, claudin and occludin gradually accumulate at ZO-1 positive spot-like junctions to form belt-like TJ.[47] Both ZO-1 and -2 associate with AJ protein α-catenin,[46,48] and ZO-1 also interacts with the GJ proteins, connexin 43[49]/45.[50] Additionally, both ZO-2 and -3 bind to actin.[51]

In Caco-2 cells, activation of JNK and c-Src lead to tyrosine phosphorylation of ZO-1 and occludin and disruption of TJ.[52] Further studies with Caco-2 cells demonstrated that reduction of p-JNK levels increased ZO-1 and occludin expression, changed their cellular distribution, and consequently enhanced the

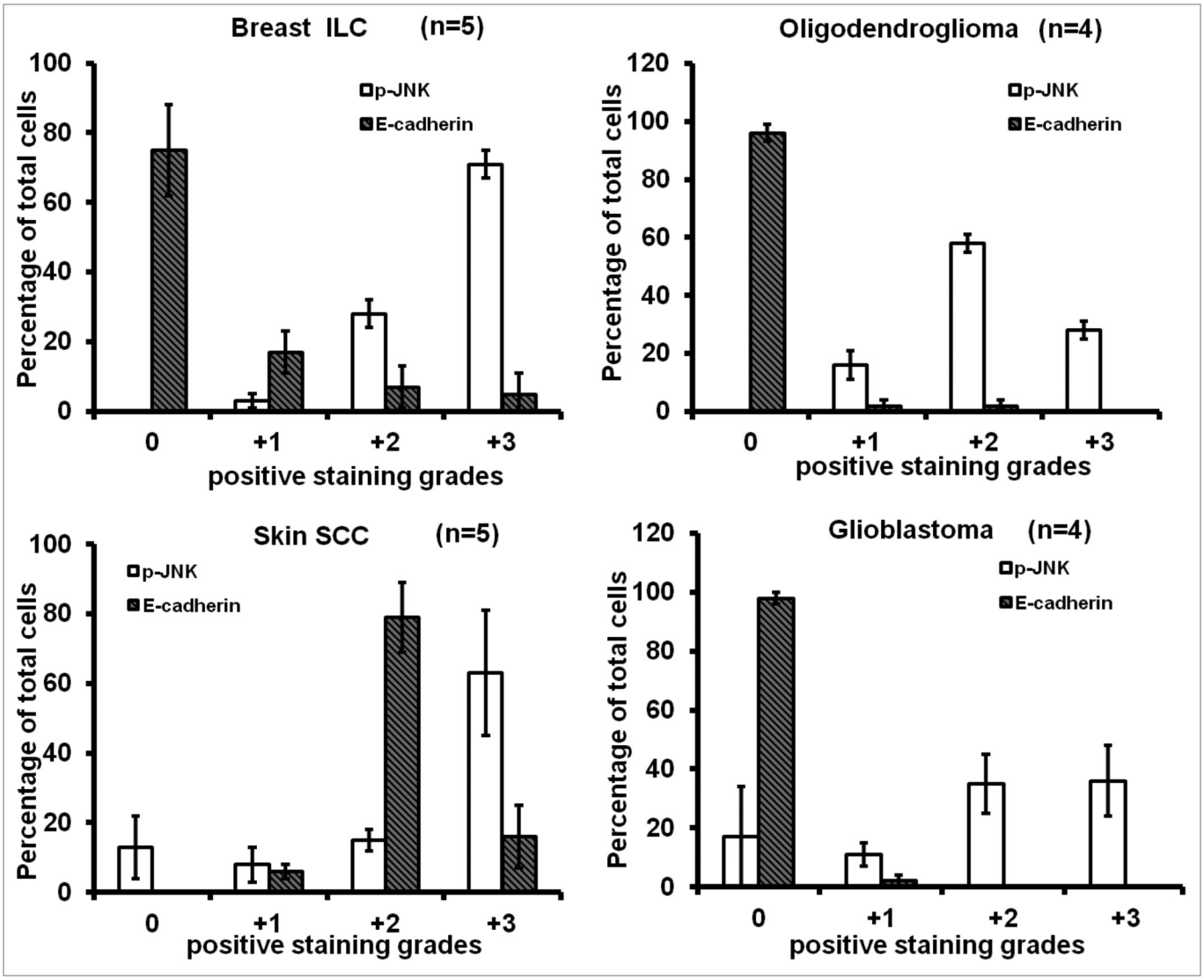

Figure 3. Analysis of tissue microarray data to uncover the correlation between p-JNK and E-cadherin levels in tumor cells. Tissues sections were graded on a 4-point scale based on the intensity of staining (from low to high 0, +1, +2, +3). The number of cells in each grade was counted using ImageJ.

transepithelial electrical resistance.[53] More detailed mechanisms have been illustrated in other cell types by Carrozzino et al. In mammary and kidney epithelial cells, inhibition of JNK activity by the chemical inhibitor SP600125 increased claudin-4 and -9 but downregulated claudin-8, leading to restriction of paracellular transport of Cl^- across the epithelial monolayer. Similarly, knocking down JNK1 or JNK2 by shRNA increased claudin-9 and decreased claudin-8 mRNA levels. Collectively, these results suggest that blocking JNK pathway decreased paracellular permeability, possibly through upregulation of claudin-9.[14]

Ex vivo studies using intestinal epithelial explants and in vivo studies using piglets supported the in vitro data. Specifically, 15-ADON (15-acetylated trichothecene mycotoxin deoxynivalenol) – a well known food contaminant that has been associated with outbreaks of gastroenteritis - activated JNK and decreased expression of claudin-3 and -4, leading to leakage of the intestinal epithelium barrier.[54] Hu et al. reported that inflammatory factors TNF-α, IL-6 and IFN-γ increased JNK phosphorylation and decreased claudin-1 and ZO-1 in the intestines of a weaning pig model.[55] However, other studies did not observe a similar correlation between JNK activation and loss of TJ. For example, side stream smoking induced JNK activation but also increased claudin-3 and ZO-2 expression in a mouse model.[56] Also, transient activation of JNK by methamphetamine did not induce loss of TJ proteins in brain microvessels.[57] Further studies employing animal models are needed to establish the relationship between JNK and TJ formation/dissolution.

Gap junctions

In contrast to AJ and TJ, GJ do not seal membranes together, nor do they restrict the passage of molecules between membranes. Rather, GJs are composed of arrays of intercellular channels that form tunnels connecting the interior of adjacent cells, and permit small molecules to transfer from one cell to another. Importantly, GJ allow ions and metabolites passing though cells

facilitating signals initiated in one cell to propagate to neighboring cells. The GJ locate in the area of two membranes that are connected by hexagonal tubes known as connexons. The major protein in purified preparations of GJ is connexin. Connexins are modified by phosphorylation, primarily on serine amino acids. Phosphorylation has been implicated in the regulation of a broad variety of processes, such as the trafficking, assembly/disassembly, degradation, as well as the gating of GJ channels.[58] Most of the studies have focused on connexin 43, which contains 21 serine and two tyrosine residues. It has been identified that connexin 43 is targeted by numerous protein kinases, such as protein kinase A, protein kinase C (PKC), p34(cdc2)/cyclin B kinase, casein kinase 1, MAPK, and pp60 (src) kinase.[59] Phosphorylation of connexin 43 by PKC caused reduction of the channel permeability[58] whereas phosphorylation by MAPK resulted in closure of GJ channels between cells.[60]

4-phenyl-3-butenoic acid (PBA), an irreversible inhibitor of peptidylglycine-α-monooxygenase (PAM), inhibited JNK activity, activated p38, increased connexin 43 expression and GJ communication in human lung carcinoma cells H2009 and ras-transformed rat liver epithelial cells.[61] In addition to epithelial cells, similar role of JNK in GJ formation was observed in cardiomyocytes. JNK activation in rat heart myocytes diminished the expression as well as the stability of connexin 43 protein, and prevented its accumulation in GJ.[62] In HL-1 cell cultures, JNK activation by anisomycin treatment led to reduction of connexin 43, which impaired cell-cell communication between atrial myocytes and ultimately prompted the development of atrial arrhythmias. These effects were prevented by the specific JNK inhibitor, SP600125.[13] An in vivo study in rabbits showed that treatment with anisomycin reduced connexin 43 by 34% and increased pacing-induced atrial arrhythmias.[13] Collectively, these studies suggest that there is an intracellular link between stress-induced JNK signaling pathway and GJ function, ultimately affecting intercellular communication and cellular behavior.[62]

JNK and Focal Adhesions

Focal adhesions (FAs), also known as cell-matrix adhesions, are large and dynamic protein complexes coupling the intracellular cytoskeleton to the surrounding extracellular matrix (ECM). The major proteins in FAs are integrins, which are heterodimers - each containing one α and one β subunit - linking ECM to intracellular actin cytoskeleton. In mammals, the combination of 19 α and 8 β subunits can form at least 25 distinct integrin receptors. The physical engagement of integrin with ECM ligands supports cell adhesion and results in generation of traction forces that modulate cell proliferation, differentiation and migration.[63]

Engagement of integrins with their ECM ligands is followed by integrin clustering leading to a sequence of intracellular responses including activation of FA proteins and associated kinases such as focal adhesion kinase (FAK), paxillin, Src-family, Abl, and Syk, Rho-family small GTPases as well as MAPK pathway kinases including ERK and JNK.[64,65] ECM molecules, such as fibronectin, laminin, vitronectin and collagen, have all been implicated in JNK activation.[66–69] Recently, a new concept of integrin cycling was described in endothelial cells, where the dynamic and constant formation of new FAs required newly engaged integrins in order to fully activate the JNK pathway.[70] In addition, it has been observed that JNK signaling could be activated by mechanical strain[71,72] and fluid shear stress through phosphorylation of FAK at Tyr-397.[73]

Conversely, JNK was shown to regulate some of the FA proteins. For example, paxillin is a multi-domain adaptor that provides multiple docking sites at the plasma membrane for FA molecules such as FAK, Src and Abl as well as actin-associated proteins such as vinculin and actopaxin.[64] Phosphorylation of paxillin at Ser-178 by JNK was shown to be essential for the formation of FAs in epithelial cells,[74,75] enabling the turnover of paxillin at the FA sites.[76] On the other hand, JNK pathway-associated phosphatase (JKAP or DUSP22) dephosphorylated FAK and suppressed cell motility.[77] However, the precise role of JNK during formation of FAs remains to be elucidated.

JNK and Cell Migration

Cell migration is a highly integrated and multi-step process that is critical for many cellular processes, including embryogenesis,[78] wound healing, angiogenesis and cancer metastasis.[79] The process of cell migration is comprised of four steps: polarization, protrusion, adhesion, and retraction.[78] The junctional complex molecules, such as cadherins, catenins, integrins and actin, participate in modulating the direction and speed of migration and regulating intracellular signaling cascades by sensing the physical and chemical cues of the local microenvironment.

Dynamic formation and dissolution of cell-cell junction is critical for migration of epithelial sheets to maintain tissue morphogenesis.[80] The role of JNK during cell migration was first reported in Drosophila.[81–83] Embryos lacking DJNK were defective in dorsal closure, a process in which the lateral epithelial cells migrate and join at the dorsal midline during embryogenesis.[82] Similarly, JNK was required for epithelial cell migration in eyelid closure during mouse development.[15,84–86]

In addition, cell motility and migration play an important role during tissue repair, e.g., epithelial sheet movement to close wounds or endothelial cell migration to form new blood vessels. In Drosophila wing and abdomen wound models, JNK signaling was required for epithelial cells at the wound edge to move and close the wound through formation and contraction of an actin cable.[16,87,88] In agreement, c-Jun, the downstream effector of JNK, was predominantly phosphorylated in cells bordering the wound, which were the cells that migrate into the wound gap.[89] JNK was also required for rapid movement of fish keratinocytes and rat bladder tumor epithelial cells (NBT-II).[74] Similarly, JNK activity was persistently enhanced in migrating epidermis at the wound site of a mouse model.[90] In another mouse model, RhoA positively regulated wound healing by upregulating the levels of p-JNK and p-c-Jun.[91] Finally, JNK was transiently phosphorylated in a mouse corneal wound model, whereas JNK inhibition suppressed epithelial spreading and wound healing in an organ-culture of mouse eyes, rabbit corneal blocks and human corneal epithelial cells.[92]

During angiogenesis, JNK was activated during migration of endothelial cells, while suppressing JNK activity using dominant negative JNK1 blocked vascular endothelial growth factor-induced endothelial cell migration.[17] Inhibition of JNK activity and siRNA knockdown of c-Jun reduced endothelial cell proliferation and migration,[93] even in the presence of JNK agonists such as TNF-α and anisomycin.[94,95] Collectively, all these studies suggest that the JNK pathway is required for cell migration during tissue development and repair. However, the detailed mechanism through which JNK interacts with junctional complexes and regulates the dynamic formation and dissolution of intercellular junctions is still under investigation.

JNK and Cancer Metastasis

The JNK signaling pathway has been implicated in invasive behavior during tumor metastasis. In a Drosophila model of invasion, JNK was involved in Src-regulated actin dynamics during invasive migration.[96] JNK2 was found to be activated in more than 70% of human squamous cell carcinoma (SCC) samples and pharmacologic or genetic inhibition of JNK2 impaired tumorigenesis of human SCC cells.[97] JNK was also implicated in several other cancers including melanoma, head and neck, breast, gastric and ovarian cancers,[98–103] suggesting that JNK may be an attractive target for cancer therapy. Indeed, suppressing expression of the oncoprotein SPAG9 diminished JNK activation in human non-small cell lung cancer (NSCLC) cells.[104] In addition, JNK inhibition by the chemical inhibitor SP600125 inhibited growth of head and neck squamous cell carcinoma,[105] whereas another JNK inhibitor, WBZ_4 was effective in inhibiting ovarian cancer in cell lines in vitro and in vivo.[106]

E-cadherin is well known for its potent malignancy suppressing, anti-metastatic activity. Sequestration of β-catenin by E-cadherin prevents the transcriptional activity of β-catenin through TCF/LEF, which among other effects, leads to androgen independent prostate cancer growth.[107,108] In many epithelial tumors such as gastric, breast, pancreatic and ovarian cancers, E-cadherin expression is partially or completely lost as they move toward malignancy.[109–115] The mechanisms for this loss include loss of heterozygosity, inactivating mutations, epigenetic silencing of the E-cadherin locus or transcriptional silencing.[116] In addition to E-cadherin and β-catenin, loss-of-function mutations in α-catenin have been found in lung, ovary, and prostate tumor samples.[117] In agreement, α-catenin expression was significantly reduced or absent in 33 of 40 human squamous cell carcinomas of the skin.[118] Although homozygous deletion of α-catenin blocked development of mouse embryos at the blastocyst stage,[119,120] conditional knockout of α-catenin in the mouse skin revealed the formation of internalized masses of hyperproliferative epithelial cells resembling squamous cell carcinomas.[121]

Interestingly, we have discovered that blocking JNK resulted in AJ formation in two carcinoma cell lines, A431 and ME180, revealing a previously unknown link between JNK and AJ.[12,35] Research work of the Xu laboratory showed a molecular link between loss of cell polarity and tumor malignancy. Mutation of different apicobasal polarity genes activated JNK signaling and downregulated the E-cadherin/β-catenin adhesion complex, which was necessary and sufficient to turn RasV12 benign eye tumors into invasive, metastatic cancers.[18,122,123] In agreement, loss of the polarity gene, *scribble*, increased expression of JNK and decreased expression of E-cadherin leading to development of invasive phenotype.[124] Transition of pancreatic tumors to metastatic cancers required JNK activation, N-cadherin upregulation and dissolution of adherens junction.[125] Mutation of casein kinase 1 epsilon promoted the Wnt/Rac-1/JNK pathways, decreased E-cadherin expression and promoted migration of breast cancer cells.[126] Collectively, these studies suggested a strong negative correlation between JNK activity and E-cadherin expression, especially during the transition of benign tumors into invasive, metastatic cancer cells. Indeed, using cancer tissue microarrays, we recently uncovered a strong negative correlation between p-JNK and E-cadherin in some aggressive cancers, such as breast invasive lobular carcinoma (ILC), oligodendroglioma, glioblastoma, and end-stage (grade-3) squamous cell carcinoma (SCC). However, the correlation was not observed in the less invasive grade-1/2 SCC (**Fig. 3**).

Conclusion and Future Perspectives

JNK plays complicated and even contradictory roles in many cellular processes, such as apoptosis, proliferation, and responses to stress from inflammatory, heat shock, and osmotic stress. Application of JNK inhibitors in inflammatory, vascular, neurodegenerative, metabolic, and oncological diseases in human has been wildly pursed.[20] However, the function of JNK serving as a regulator of AJ, TJ, and GJ is currently being uncovered.[12,35–37] In vitro traditional 2D cultures, 3D bioengineered tissues as well as in vivo studies have implicated JNK in regulation of cell-cell junction formation, in biological processes requiring dynamic formation and dissolution of junctions, such as development, wound healing, angiogenesis and cancer metastasis. More studies are necessary to reveal the molecular mechanisms through which JNK regulates junction formation and intercellular adhesion in normal or pathological disease states.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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