Review

Cancer Research

JNK-Induced Apoptosis, Compensatory Growth, and Cancer Stem Cells

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Abstract

Overwhelming evidence suggests that c-*jun*-NH_2-kinases (JNK) are a set of key stress-responsive kinases that mediate cell apoptosis, which is an important process for tumor suppression. However, JNKs have also been implicated in the malignant transformation and tumorigenesis of cells. This review attempts to reconcile these 2 contradictory functions of JNKs with recent discoveries on the role of JNKs in compensatory growth of neighboring cells and stem cells, which may provide new mechanistic understanding about the role of JNKs in the regulation of cancer stem cells and the pathogenesis of cancers. *Cancer Res; 72(2); 379–86. ©2012 AACR.*

Introduction

In the past few years, a new concept in tumorigenesis, the cancer stem cell (CSC), has emerged (1). It is believed that CSCs are a population of rare cells that are capable of initiating and maintaining the tumor, differentiating into endothelial cells for tumor vascularization, and allowing the propagation and colonization of tumor cells at sites distant from the original tumor location. Similar to normal stem cells, CSCs retain the properties of self-renewal and multilineage differentiation. However, these cells distinguish themselves from normal stem cells by maintaining their malignant potentials, such as a loss of both the genomic integrity and epigenetic identity of the normal stem cells. An unsolved issue in CSC theory is whether CSCs are truly stem cells or if they are non–stem cells in which the self-renewal is activated by oncogenic mechanisms.

The c-*jun*–NH_2–kinases (JNK) are protein kinases involved in cellular stress response, apoptosis, and malignant transformation (2–4). They regulate a wide spectrum of intracellular signaling pathways that converge to regulate both gene expression and the homeostasis of macromolecules, including mRNAs and proteins (5). In the human genome, 3 genetic loci encode JNK1, JNK2, and JNK3, each of which has 2 to 4 isoforms that result from the alternative splicing of the corresponding pre-mRNAs. Both JNK1 and JNK2 are ubiquitously expressed, whereas JNK3 is expressed predominantly in the brain and, to a lesser extent, in the heart and testis (2, 4). JNKs have a well-documented functional redundancy to phosphorylate their cognate and noncognate substrates, which include c-Jun, JunD, ATF2, polycomb repressive complex 1 (PRC1) subunit Bmi1 (6), Akt (7) FoxO4, PPARγ1, c-Myc, p53, NFATc2, STATs (8), IRS-1, Itch, 14-3-3, histone H3 (9), SIRT1 (10), and other proteins (5). However, evidence also implies that JNK1, rather than JNK2 or JNK3, is the key JNK family kinase responsible for the phosphorylation of c-Jun on serines 63 and 73 and for the expression of RNA polymerase III (11, 12). In myoblast cells, JNK1, but not JNK2, mediates TNFα-induced cell proliferation by inhibiting myoblast cell differentiation and promoting the generation of inflammatory cytokines such as interleukin-6 (IL-6) and leukemia inhibitory factor (13). In addition, the importance of JNK1 over JNK2 was shown in the pathogenesis of several human diseases, including diabetes, lung fibrosis, and cancer (14). Furthermore, gene knockout studies in mice revealed that JNK1 is the most important JNK family kinase for the proliferation of the CD8+ T cells (15) and for neural development (16, 17).

JNK1 and JNK2 in Carcinogenesis

Although JNKs are primarily attributed to proapoptotic cell death or tumor suppression in response to a variety of stress, inflammatory, or oncogenic signals (18), emerging evidence suggests that JNKs, especially JNK1, play a role in the malignant transformation of cells and in tumorigenesis. For example, the genetic disruption of the jnk1 locus in mice decreased the susceptibility to a Bcr-abl–induced lymphoma (19). In UV-induced tumorigenesis, activation of JNK1 is essential for the cell transformation and proliferation in response to the oncogenic Ras signal (20). In cells derived from the soft tissue of a childhood sarcoma, silencing of JNK1, but not of JNK2, by siRNA repressed the growth of these tumor cells, indicating that JNK1 is proproliferative, whereas JNK2 might be proapoptotic (21, 22). JNK1 has been viewed as a pivotal kinase that promotes the development of tobacco smoke–induced lung tumors, because the ablation of JNK1 alone reduced the effect of tobacco smoke on both the lung tumor multiplicity and the tumor size (23). Animal models of gastric cancer also showed that JNK1 contributes to the development of gastric tumors that are induced by the chemical carcinogen *N*-methyl-*N*-nitrosourea (24). The most compelling evidence for the role of JNK1 in cancer initiation is from studies of hepatocellular

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carcinoma (HCC) in both human and animal models. By using human HCC tissue samples that were case matched with the adjacent noncancerous liver tissues, 2 independent studies found that more than 50% of the HCC samples exhibited a higher activation of JNK1, but not of JNK2 (25, 26). Additional studies further revealed that higher JNK1 activation was associated both with a poorer prognosis in patients and with overexpression of several hepatic stem cell or progenitor cell markers, such as EpCAM, CD24, CD133, KRT19, and AFP (27). In mouse HCC models, genetic disruption of the jnk1 locus substantially reduced the number and size of HCCs that were induced by diethylnitrosamine (DEN; ref. 25). JNK1 has also been shown to be an essential kinase for mediating the development of HCC due to a hepatocyte-specific deficiency of IKKβ or IKKγ, which are the key subunits of the IKK kinase complex for NF-κB signaling in mice (28–30).

JNK-Induced Compensatory Proliferation Links Apoptosis to Carcinogenesis

Overwhelming evidence has unequivocally unraveled the role of JNKs, especially JNK1, in cell apoptosis or tumor suppression (31–33). The proapoptotic or tumor suppressor–like function of JNK1 was revealed even in studies that showed an oncogenic effect of sustained JNK1 activation in animal cancer models (25, 28). How can we reconcile these 2 contradictory functions of JNK1? A growing consensus is that the evasion of apoptosis is one of the hallmarks of cancer (34, 35). Accordingly, it is tempting to attribute this defect in apoptosis to the oncogenic role of JNKs, despite reports suggesting that the major apoptotic signaling pathways, CD95 (Fas) and CD95 (FasL), are required for the optimal growth of ovarian cancer, liver cancer, and glioblastoma in animal models (36–38). In addition to the possibility that JNKs can directly induce growth signals at the same time as inducing apoptosis, it is possible that a compensatory proliferation of neighboring cells might be triggered by the apoptotic, stressed cells. In other words, the compensatory growth might be an essential linker to bridge apoptosis and carcinogenesis.

JNK-induced compensatory growth in *Drosophila*

How JNK1-mediated cell death triggers compensatory proliferation of neighboring cells is not fully understood. The key evidence for compensatory proliferation induced by JNK-activated cell death is from studies in *Drosophila* (39, 40). After apoptosis was initiated by disrupting the antiapoptotic signal from diap1 [X-linked inhibitor of apoptosis (XIAP) in mammals] and the activation of the effector caspase was blunted to create "undead" cells in the *Drosophila* larval imaginal discs, an overgrowth of neighboring, normal cells was observed (39). Biochemical studies found that these undead cells were able to secrete wg and dpp mitogens (the Wnt and BMP orthologs of mammalian cells, respectively) in a JNK-dependent manner.

The Wnt and BMP proteins have long been viewed as key signaling proteins involved in embryonic development, cell proliferation, oncogenesis, and stem cell maintenance (41). Thus, it is very likely that wg (Wnt) and dpp (BMP), the secreted glycoproteins from the stressed cells in which JNK is activated, are the master regulators for the JNK-induced compensatory proliferation of the neighboring cells. The affected neighboring cells can be either the same lineage as the stressed cells or a different lineage. The degree of the compensatory proliferation might be dictated by both the intrinsic Wnt- and BMP-responding pathways and the differentiation states of the affected cells. A number of reports have suggested that Wnt and BMP stimulate cell growth and tissue regeneration in vertebrates and insects by cooperating with or inducing the Janus-activated kinase (JAK)/STAT– and/or the β-catenin/T-cell factor (TCF)–signaling pathways (42–44). Additionally, wg signaling is capable of repressing Notch activity, which leads to the expression of *dmyc* and the microRNA *bantam*, which both promote cell growth by affecting the G_1 to S-phase transition of the cell cycle (45).

In addition to wg and dpp, JNK-dependent activation or induction of the JAK/STAT pathway might also be involved in the undead-cell– or tissue-damage–induced compensatory proliferation of normal cells in *Drosophila* (46, 47), which could explain the compensatory growth in *Drosophila* with the loss-of-function mutations of wg, dpp, or both wg and dpp (48). Unlike its mammalian counterparts that contain multiple isoforms of all of the major JAK/STAT pathway components, the *Drosophila* genome encodes only 1 JAK (HOP) and 1 STAT (STAT92E) molecule (49). The evidence suggesting that the constitutive activation of JAK/STAT signaling causes cancer has long been established in both human and *Drosophila*. A gain-of-function mutation of the *Drosophila* HOP (JAK) protein resulted in the overproliferation of the larval blood cells and subsequent melanotic tumors (50). In the midgut of *Drosophila*, a tissue injury induced by bleomycin activates JNK, which in turn induces a rapid translocation of the Yorkie (Yki, the mammalian Yap homolog) protein from the cytoplasm to the nucleus. As a cofactor for transcriptional regulation, the nuclear translocated Yki is capable of upregulating the expression of the Unpaired family of cytokines (Upd, Upd2, and Upd3, the IL-6 orthologs of mammalian cells) and the activation of JAK/STAT signaling (51). In resting cells, Yki is predominantly localized in the cytoplasm because of its phosphorylation by the tumor suppressor Hippo (Hpo)/Wts. It is unclear how JNK impinges upon Hpo/Wts to activate Yki. One of the potential mechanisms might be that JNK directly phosphorylates and inactivates Hpo or Wts. However, it is also possible that JNK may phosphorylate Yki to antagonize the phosphorylation and inactivation of Yki by Hpo/Wts. In apoptotic conditions, JNK-dependent activation of Yki and the consequent release of the Upd cytokines from the stressed cells are pivotal factors for the compensatory overgrowth of the nonapoptotic compartment (52).

Both the wg/dpp and JAK/STAT signaling pathways are essential factors for the self-renewal of intestinal stem cells (ISC) in the midgut of *Drosophila* (42, 51, 53–55). This finding raises an interesting question about whether the compensatory growth is a result of the overproliferation of the stem cells to replenish the damaged cells in response to stress or tissue injury. It is well recognized that adult stem cells are responsible for replenishing the dead cells to maintain the homeostasis of the normal tissues. Earlier studies showed a contribution of

JNK activation in the intestinal absorptive enterocytes to the compensatory division and/or differentiation of ISCs in circumstances such as infection, chemical damage, or mechanical damage (56, 57). Through asymmetrical division, *Drosophila* ISCs give rise to an ISC and an enteroblast cell, which can then further differentiate into 2 major types of intestinal epithelial cells, enterocytes and secretory enteroendocrine cells. The activation of JNK in enterocytes by silencing of the JNK suppressor, puckered (puc), or expression of the active form of hemipterous [Hep, *Drosophila* JNK kinase (DJNKK)] resulted in a substantial increase in both the Upd cytokines and in the number of ISCs (51, 56). It is believed that upon JNK activation in the enterocytes, the released Upd cytokines engaged with the IL-6R–type receptor Domeless (dome) on the surface of ISCs, which led to the activation of the JAK/STAT signaling in ISCs, followed by a dramatic increase in the mitotic index of the ISCs. Similarly, paracrine wg from the circular muscles next to the ISCs had been implicated as an external niche signal that is important for the self-renewal of ISCs (54). In addition to the paracrine role of wg/dpp and the Upd cytokines from the stressed enterocytes that are induced by JNK activity on ISCs, JNK activity within the ISCs themselves seemed to be critical for the ISC proliferation when the *Drosophila* were challenged with paraquat or bleomycin (58). In this scenario, JNK- and extracellular signal-regulated kinase (ERK)–dependent phosphorylation of the FOS protein within the ISCs is sufficient to promote the stress-induced ISC proliferation, which may occur through the AP-1–dependent transcriptional regulation of several genes that drive the cell-cycle transition.

JNK-induced compensatory growth in animal disease models

Whereas the majority of studies on JNK-regulated compensatory proliferation were done in *Drosophila*, reports suggest that JNK is a key contributor to the compensatory proliferation of hepatocytes in a mouse HCC model with an IKKβ deficiency (28, 30). Mice with a hepatocyte-specific disruption of the IKKβ gene exhibited a substantial increase in cell apoptosis, reactive oxygen species production, and JNK activation in hepatocytes in response to DEN treatment. Meanwhile, these mice also showed a marked enhancement in hepatocyte proliferation and carcinogenesis induced by DEN. Such effects were prevented in progenies from cross-breeding these mice with JNK1 knockout mice, suggesting that JNKs, especially JNK1, play a central role in hepatocyte apoptosis and in the compensatory proliferation of nonapoptotic cells. Similar findings were observed in murine liver tumor models with a hepatocyte-specific IKKγ/NEMO or TAK1 deficiency (29, 59). It was originally hypothesized that this compensatory proliferation was induced by the growth factors released from the Kupffer cells. Alternatively, it is possible that mitogens released from the apoptotic hepatocytes in which JNK is activated induce the compensatory proliferation of the nonapoptotic hepatocytes.

A Potential Role of JNK in Cancer Stem Cells

As links were revealed between JNK activation and wg/dpp or JAK/STAT signaling in tissue damage– or stress-induced compensatory proliferation, it is plausible to hypothesize that some human cancers are formed as a result of the compensatory overgrowth of stem cells (Fig. 1). Either wg/dpp or JAK/STAT, which are both regulated by JNK activation, can provide a suitable niche for the dynamic proliferation of stem cells. Sustained activation of JNK will cause the aberrant generation of the wg/dpp and JAK/STAT signals, which will be potentially dangerous for either the overcompensatory proliferation of tissue stem cells or, alternatively, for the oncogenic transformation of stem cells. It is also possible that a prolonged activation of such signals in non–stem cells might cause *trans*-differentiation of these cells into CSCs. Although the specific contributions of JNK, Yap (Yki in *Drosophila*), Wnt/BMP (wg/dpp in *Drosophila*), and JAK/STAT signaling to stem cell overgrowth and cancer in vertebrates remain to be established, we expect that similar signaling pathways and their regulatory effects on stem cells might be involved in the development of murine or human cancers. Indeed, the augmentation of JNK signaling via the transgenic gut-specific expression of constitutively active JNK1 in mice significantly increases ISC proliferation and villus length (60). Remarkably, convergence seems to occur between JNK signaling and Wnt signaling in which the activation of JNK not only induces the expression of c-Jun, cyclin D1 and CD44, and the classic JNK target genes (Fig. 1) but also upregulates the mRNAs of some of the Wnt target genes, including *tcf4*, *axin2*, and *lgr5* in crypt base columnar cells, a group of intestinal cells with stem cell–like properties (61). In the case of the JNK-dependent expression of lgr5, a CSC marker of colon cancer, it was suggested that the phosphorylation of c-Jun by JNK prevents c-Jun from recruiting the Mbd3/NuRD transcription repressor complex at the promoter region of the *lgr5* gene (62). Furthermore, in a mouse Apc mutation model, JNK activation was not only associated with enhanced Wnt signaling from the loss of Apc, but it also promoted mTORC1 activation, which led to a translational upregulation of the proteins necessary for intestinal tumorigenesis (63). Thus, these data clearly indicate that JNK signaling, compensatory overgrowth, and stem cell proliferation are shared mechanisms for tumorigenesis between invertebrates and vertebrates.

Several lines of evidence also support the notion that JNK and its regulation of Wnt and JAK/STAT signaling are critical for cancer development in mammals, although the stem cell hypothesis in this JNK-mediated process has not been tested directly. First, a number of human cancers exhibit enhanced activation and/or increased expression of JNK, Yap, IL-6, STAT3, Wnt, or TGFβ (2, 64). Second, the JNK1-dependent compensatory proliferation has been viewed as a key mechanism in the mouse model of HCC with a hepatocyte-specific deletion of the IKKβ or IKKγ gene (28, 29). Lastly, both the STAT3- and Wnt-signaling pathways have been viewed as important regulators for maintaining the self-renewal of CSCs in some experimental cancer models (65, 66). Both Wnt and BMP, the downstream targets of JNK signaling, have been shown to be important for the self-renewal of many stem cells, including embryonic stem cells (ESC), lineage-specific stem cells, and CSCs (67–70). The transgenic overexpression of *wnt1* in mice induces a mammary tumorigenesis with an increased

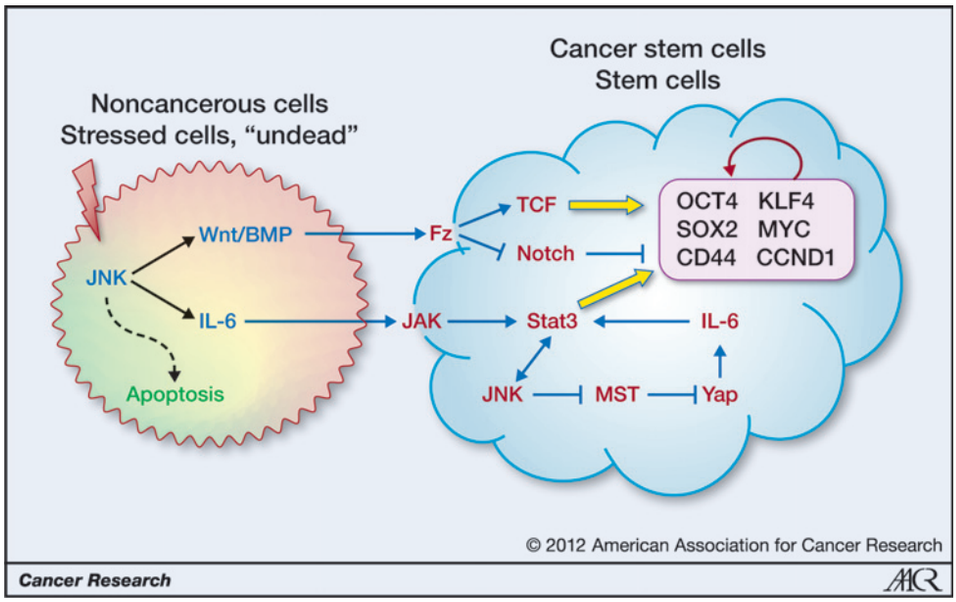

Figure 1. JNK signaling enhances the compensatory proliferation of the neighboring cells, stem cells, or CSCs. In response to stress signals, activated JNK induces the release of Wnt/BMP and IL-6 from the stressed cells in which an apoptotic response might be initiated but not yet completed, thus inducing a state of "undead" cells. The released Wnt/BMP and IL-6 interact with Fz and JAK complexes, respectively, on the surface of the neighboring cells, stem cells, or CSCs, which is followed by the activations of the β-catenin/TCF– and Stat3-signaling pathways in these cells. Both β-catenin/TCF and Stat3 are capable of enhancing the expression of the genes such as CCND1, OCT4, Sox2, KLF4, c-Myc, CD44, and others that are important for the cell proliferation and self-renewal of the stem cells or CSCs. Reciprocal positive feedback exists between Stat3 and JNK signaling in the nonstressed neighboring cells or stem cells. Alternatively, JNK can affect Stat3 through the suppression of Hpo/Wts (MST/LATS in mammals) to alleviate Yki (YAP in mammals), which can induce Stat3 through IL-6 signaling. Similarly, in addition to regulation of the β-catenin/TCF pathway, Wnt signaling can regulate cell growth of stem cells by suppressing Notch, a repressor of c-Myc and other cell-cycle genes. Circled arrow indicates a group of genes important for the self-renewal of the stem cells or CSCs.

number of CSCs (71). In a cell culture model, the addition of the exogenous Wnt protein is sufficient for the expansion of mammary stem cells for many generations (72). The importance of Wnt signaling in mouse or human ESCs also provided complementary support for the potential of JNK and Wnt in CSCs. Wnt signaling is believed to maintain self-renewal of stem cells by cooperating with or enhancing the function of several stem cell transcription factors such as Oct3/4, Sox 2, and Nanog (73). In contrast, BMP signaling induces differentiation of human ESCs by limiting the activity of Nanog (74).

The notion that JNKs might be involved in regulation of CSCs in human cancer is reinforced by findings indicating an association between JNK or IL-6 and CSC markers in human HCC (27, 75, 76). Accumulating evidence suggests that the most common etiologic factors in HCC are chronic inflammation of the liver due to hepatitis-B virus or hepatitis-C virus infection or exposure to environmental carcinogens. IL-6, the key inflammatory cytokine, had been viewed as a central molecular linker between chronic liver inflammation and HCC. Clinical data clearly show an elevated blood IL-6 level in male HCC patients (77). Animal studies using IL-6 knockout mice showed a nearly complete inhibition of HCC development in mice treated with DEN (78). Positive feedback between JNK and IL-6 has been observed in an obesity-induced HCC model (79). As a preferential activator of STAT3 signaling, IL-6 is capable of inducing the expression of JAK/STAT3 target genes such as VEGF, Bcl-xl, cyclin D1, matrix metalloproteinase, and others for the sustained proliferation of hepatocytes and hepatic CSCs (Fig. 1; refs. 76, 80). Notably, genes downstream of IL-6 were enriched in the surrounding noncancerous liver tissue of HCC patients with the poorest survival rates (81), which might indicate a compensatory proliferation of HCC cells or CSCs induced by IL-6 from adjacent tissues with chronic inflammation.

A potential link between JNK1 and HCC progenitor cells or CSCs was revealed in a gene-profiling study based on collected human HCC tissues that were stratified by their JNK1 activation levels (26, 27). The genes with signatures corresponding to both poor HCC prognosis and hepatoblastoma, an embryonic liver tumor that features liver progenitor cells or CSCs, were enriched in HCCs that had higher JNK1 activation (27). A reanalysis of the gene-profiling data in previous studies (26, 27) indicates that many important genes for CSCs are highly expressed in HCCs with higher JNK1 levels, including *CD24*, *CD44*, *CD133*, *Stat3*, *GPC3*, *EpCAM*, *KRT19*, *KRT7*, *SOX4*, *Tet1*, *Runx1*, *Runx2*, *Wdr*, *Seme6A*, *JARID1a*, and *JARID1b*. These data clearly suggest an important role for JNK1 regulation of HCC progenitor cells or CSCs.

JNK Activation in the Stemness of Embryonic Stem Cells

The data derived from studies in *Drosophila* and some human cancers indicate that JNK might be a regulator of stem cells or CSCs. The embryonic lethality of JNK1 and JNK2 double-knockout mice suggests that JNK kinases are essential

for embryonic development (16). Because of the central role of ESCs in the development of the embryo, an important concept to examine is whether JNKs play a role in the establishment, maintenance, and differentiation of ESCs. Several protein kinase pathways had been implicated as pivotal regulators for the self-renewal, proliferation, or differentiation of ESCs, including phosphoinositide 3-kinase (82), receptor and nonreceptor tyrosine kinases (83), and others. However, to date, a systematic study of the role of JNKs in certain aspects of ESCs, such as self-renewal, maintenance of stem cell totipotency, and differentiation, has not been done. Uncertainties and controversies remain about whether JNKs are required for the proliferation or differentiation of mouse ESCs (mESC). In testing the toxicity of the carcinogenic metal chromium [Cr(VI)], Xia and colleagues showed that JNKs protect mESCs from Cr(VI)-induced cytotoxicity and suppress the differentiation of mESCs or the derived embryonic bodies (84). Similarly, JNK signaling seems to be important for the proliferation of mESCs by collaborating with the Akt-mTOR pathway in response to zinc stimulation (85). Furthermore, in a recent study designed to determine how an essential amino acid, L-threonine, regulates mESCs, Ryu and Han showed that JNK is one of the key kinases necessary for the self-renewal and proliferation of mESCs (86). The addition of the JNK inhibitor SP600125 blocked the L-threonine–induced expression of the stem cell marker OCT4 and several cell proliferative molecules, such as cyclin D1, cyclin E, and c-Myc (86).

In contrast, an earlier study that investigated the neurogenesis of JNK1-deficient mESCs found that a deficiency of either JNK1 or JNK2 had no effect on the expression of the mESC markers or the self-renewal of the mESCs (87). However, JNK1 deficiency clearly impaired the neural differentiation of mESCs, because JNK1 was required for the transcriptional expression of a neural-specific gene, the neurofilament light chain, in response to nerve growth factor. That study also suggested that JNK1 might facilitate mESC differentiation by inhibiting Wnt-4 and Wnt-6, which are 2 key Wnt-signaling molecules in vertebrates. The concept that JNKs are involved in the differentiation of mESCs was supported by another study showing that JNKs are required for lineage-specific differentiation but are dispensable for the self-renewal of mESCs (88). These results seem to contradict what had been found in the intestinal cells of *Drosophila* and mouse (39, 60).

Unlike what has been found in mESCs, the potential role of JNKs in the self-renewal of human ESCs (hESC) seems to be straightforward (89–91). Interrogation of the phosphoproteomes of the hESC line WiCell's H1 by identifying phosphorylated peptides via multidimensional liquid chromatography/mass spectrometry, Ding and colleagues observed significantly elevated JNK activity in undifferentiated hESCs (89). This observation was further supported by the treatment of undifferentiated hESCs with the JNK inhibitor SP600125 or with a JNK inhibitor III polypeptide. Inhibition of JNK by either SP600125 or JNK inhibitor III caused the differentiation of the hESCs and the substantially reduced expression of NANOG and OCT4, which are 2 important markers of undifferentiated hESCs. The possible contribution of JNK signaling to the maintenance and/or self-renewal of hESCs was additionally confirmed in a different hESC line, Harvard's HUES-7, by the stable isotope labeling of amino acids in cell culture combined with liquid chromatography/tandem mass spectrometry (91). JNK1 activity and the activity of other kinases, including cyclin-dependent kinase 1/2 (CDK1/2) and mitogen-activated protein kinase 14 (MAPK14; p38α), was overrepresented in hESCs. In response to the BMP-induced differentiation, a transient elevation of c-Jun phosphorylation was observed, which indicated both the competence of the basal JNK pathway to maintain the stemness of the hESCs and the possible involvement of JNK activation in the initiation of hESC differentiation. Furthermore, as determined by electron transfer dissociation-based large-scale tandem mass spectrometry, the MAPK pathway seems to be 1 of the top 3 signaling pathways in another hESC line, although the activated MAPK pathway was not defined among the ERK, JNK, or p38 pathways (92).

The comprehensive analyses of the hESC transcriptome provided corroborating evidence for the role of JNK signaling in the self-renewal and/or pluripotency of hESCs (93, 94). Both jun and fos, 2 JNK target genes, have been found to be signature genes in several tested hESC lines (95). Additionally, analysis of the gene expression dynamics of the hESCs showed that the expression of some of the JNK-signaling molecules was significantly higher in the undifferentiated hESCs than in the differentiated hESCs (94). These JNK-signaling molecules include the JNK target gene Jun and 2 upstream kinases of JNK, MAP4K1 (MEKKK1) and MAP3K7 (TAK1). Both MAP4K1 and MAP3K7 are preferential upstream kinases for the activation of JNK (96, 97). Differentiation of the hESCs by removal of both the feeder cells and basic fibroblast growth factor (bFGF) resulted in the downregulation of these JNK-signaling molecules (94).

In accordance with these observations, recent genome-wide RNA interference screening in hESCs showed that the genes of several of the JNK-signaling molecules, such as MEKK3, MEKK4, MEKK8, JNK3, and Fos, contain binding sites in their promoter or enhancer regions for PRDM14, which is a stem-cell–specific transcription factor (98). ChIP-seq analysis showed direct binding of PRDM14 to the regulatory regions of these genes. PRDM14 not only upregulates the expression of Fos but also inhibits DUSP10 and DUSP12, the negative regulators of JNK signaling. In mESCs, PRDM14 overexpression can enhance the activity of NANOG to prevent the mESC differentiation of the extraembryonic endoderm (99), which provided complementary evidence indicating a possible role for JNK signaling in the maintenance of the ESCs.

JNKs in Adult Stem Cells

Although the function of JNKs in the proliferation and/or self-renewal of hESCs is noteworthy, it is also of interest to investigate the role of JNKs in the proliferation of human adult stem cells, such as adipose-derived stem cells (100) and mesenchymal stem cells (MSC; ref. 101). Evidence indicates that JNK activation is essential for the injury-induced proliferation of the adipose-derived stem cells and the release of several angiogenic factors and growth factors such as platelet-derived growth factor, VEGF, and hepatocyte growth factor. The inhibition of JNK activity using a chemical JNK inhibitor not

only repressed the release of those growth factors but also reduced the number of the cells harboring the stem cell marker CD34 (100). MSCs can differentiate into mesenchymal lineage cells such as osteoblasts, chondrocytes, and adipocytes. MSCs have also been thought to be the progenitor cells for some human cancers. In an attempt to determine the contribution of MAPKs to the growth factor FGF-induced MSC proliferation, studies by Ahn and colleagues showed that JNK, but not ERK or p38, is critical for the proliferation of the MSCs in response to FGF (101).

Conclusions

Despite varying opinions among researchers in the field, revealing the role and regulation of intracellular signaling pathways is undoubtedly the most important task in understanding how the capacity for both the self-renewal and multipotency of a given stem cell is maintained. It is known that epigenetic modifications, especially modifications of the histone proteins, determine the accessibility of the chromatin for the differentiation programs to produce divergent cell types. Accordingly, any signaling that occurs to maintain the stemness of a cell must be achieved by the epigenetic activation of the stemness programs and the termination of the differentiation programs. In addition to the JNK-regulated signaling pathways discussed above, JNKs have also been implicated in the phosphorylation of histone H3 serine 10 and serine 28 (102), which affects the binding of the trithorax and PRC2 to chromatin and, thus, the propagation of active and silent chromatin, respectively. Furthermore, JNKs or JNK-signaling molecules have been implicated in the antagonizing of the PRC complexes formation of a permissive chromatin structure on some of the genes that are involved in cell growth and lineage development (6, 103). Important issues about the mechanism by which JNKs affect the balance between the stability and plasticity of stem cells must now be addressed. A critical question is whether JNKs are essential kinases for the multipotency of stem cells or whether the kinases are required for the earlier differentiation of stem cells. It might be overreaching to claim that JNKs are the central kinases for the key properties of stem cells. However, it would be fair to state that JNKs are critical kinases in concert with other key signaling molecules or transcription factors that govern the development and fate of stem cells and CSCs.

The achievement of effective cancer treatments remains a challenge. Some of the new treatment strategies, such as personalized medicine, are too cumbersome to be scaled up. Because cancers very frequently originate from CSCs, the targeting of a particular signaling pathway, such as JNK, in CSCs might circumvent some of the setbacks that conventional therapies currently face, such as fast relapse and chemoresistance. The significance of stem cell research is its promise for the stem cell–based treatment for some degenerative diseases or for cancer. The recently recognized tumorigenic nature of hESCs, adult stem cells, and induced pluripotent stem cells has put stem cell–based therapies in jeopardy. It is plausible to assume that this tumorigenicity of stem cells might be a consequence of aberrant JNK activation. Thus, the inhibition of JNK will not only force the differentiation of stem cells to replace damaged tissues but also reduce the tumor burden in cancer patients by eliminating CSCs. Recent evidence has shown that the administration of an inhibitor against the downstream target of JNK, JAK, is clinically beneficial in treating some forms of myeloproliferative neoplasm (104). Accordingly, a JNK-based therapeutic strategy that targets CSCs for cancers could be developed in the foreseeable future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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