Association of NEDD9 with TGF-β-triggered epithelial-mesenchymal transition and cell invasion in prostate cancer cells: implications for cancer aggressiveness

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NEDD9 belongs to the Cas (Crk-associated substrate) family, proteins of which mediate downstream signaling processes including cell-cycle, tumorigenesis and cytoskeletal organization. In epithelial-mesenchymal transition (EMT), NEDD9 plays an important role, but the functional mechanism underlying NEDD9-mediated EMT in prostate cancer (PCa) remains uncertain. Recently we confirmed that NEDD9 is predominantly involved in TGF-β-mediated EMT and cell motility in PCa cells. We herein discuss the functional role of NEDD9 in terms of pathogenesis of PCa.

Keywords: EMT; NEDD9; Prostate cancer; TGF-β; miR-145; ubiquitination; phosphorylation

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Introduction

Epithelial-to-mesenchymal transition (EMT) is an important mechanism for cancer metastasis and invasion. Epithelial cancer cells activate embryonic processes of epithelial plasticity and change from a polarized, epithelial phenotype to a mesenchymal phenotype with increased motility, referred to EMT [1-4]. While EMT is proceeding, epithelial cells obtain various biological changes including expression of mesenchymal biomarkers, induction of angiogenesis, forced resistance to apoptosis, and increased production of extracellular matrix components. First, extracellular proteases such as matrix metalloproteinases (MMPs) degrade collagen fibers of the basement membrane of primary cancer tissues. Subsequently, cancer cells infiltrate into the surrounding vessels, and finally metastasize to preferable organs through the cardiovascular and lymphatic systems.

Thus, interpretation of the functional molecules that regulate EMT in aggressive PCa may be useful for the development of targets to treat metastasis of PCa and inhibit the progression of localized PCa to a metastatic state.

NEDD9 (neural precursor cell-expressed developmentally downregulated protein 9), also known as HEF1 (human enhancer of filamentation1), belongs to Cas family proteins including CASS4/HEPL and BCAR1/p130Cas, which have been implicated as signaling mediators of various biological events including cell cycle, cell attachment, apoptosis, anoikis, motility, and tumorigenesis [5-9]. In various human cancer types including lung cancer, glioblastoma and melanoma, it was showed that the levels of NEDD9 expression had positive correlation with poor prognosis and advanced-stage disease [10-13]. In a transgenic mouse model with the MMTV-polymavirus middle T, early tumor growth was significantly reduced by genetic ablation of...
NEDD9 \[14\]. Recently, it was reported that exogenous overexpression of NEDD9 altered the expression of EMT associating molecular markers and enhanced cellular invasion and migration, concomitant with increased levels of Snail/Slug, initial EMT transcriptional factors, via activation of MAPK/ERK signaling in breast cancer cells \[15\]. Conversely, PCa has a strong potential for bone metastasis as does breast cancer, but the characteristic molecular functions of NEDD9 has remained unclear in PCa.

Transforming growth factor-β (TGF-β) is a major extracellular inducer of EMT \[16\]. Tumor invasion can be driven locally through induction of EMT or angiogenesis by TGF-β \[16,17\]. TGF-β is also abundant in the bone matrix, and is robustly freed into the microenvironment of bone metastatic sites through bone resorption \[18\]. Under this condition, both bone cells (osteoblasts and osteoclasts) and metastatic cancer cells accelerate osteoblastic and/or osteoclastic change and cell proliferation, and lead to the appearance of skeletal-related events (SRE) associated with bone metastases \[19\]. As regards the initial mechanisms of action in the cancer metastatic cascade, EMT processes are reported in several studies to be mainly involved in increased cell invasion, migration and intravasation. In the bone microenvironment, numerous EMT effectors including TGF-β, IGF, Wnt, HGF, PDGF and hypoxia, have been identified and encourage the formation of bone metastases. In advanced PCa, TGF-β expression is markedly increased in PCa and the circulation, concomitant with a negative correlation of its expression level with the prognosis of PCa patients \[20\].

In our recent study, we investigated in PCa cells the effect of NEDD9 knockdown on both the cell invasion and the EMT process induced by TGF-β \[21\]. By knockdown of endogenous NEDD9 expression, phosphorylated ERK and Snail/Slug expression was clearly suppressed and the E-cadherin level was subsequently enhanced regardless of treatment with TGF-β and tumor invasion triggered by TGF-β was also suppressed, concomitant with a molecular action to reverse EMT (namely mesenchymal-to-epithelial transition; MET) in PCa cells. Based on these experimental data, a NEDD9-mediated signaling pathway may be dominant in regulating cell motility and the process of EMT.
induced by TGF-β in PCa cells. Furthermore, we performed immunohistochemical (IHC) analysis to evaluate NEDD9 protein expression in paraffin-embedded prostate tissue sections. In IHC analysis, NEDD9 expression was upregulated in PCa tissues, compared with normal tissues without neoplasia. In the specimens of PCa, the expression level of NEDD9 was positively correlated with the serum total PSA level and Gleason score respectively. Moreover, the expression of NEDD9 was significantly increased in primary PCa samples with bone metastasis, compared with those without bone metastasis. Based on these IHC results, we consider that NEDD9 expression could be a brand new biomarker to grade the progressiveness of PCa and to anticipate bone metastasis.

We speculate that NEDD9 is a major mediator of EMT upon stimulation with TGF-β in PCa. In the case that NEDD9 expression is regulated appropriately, both distant metastasis from primary PCa and secondary extension from metastatic bone microenvironments may be suppressed.

Recently, human microRNA-145 (miR-145) which is one of the small regulatory RNAs, was reported in glioblastoma cells to downregulate NEDD9 expression and to inhibit the cell invasion [13]. MiR-145 has been identified as a regulator of several genes implicated in apoptosis, differentiation, motility and cell proliferation in several types of cancers [22-26]. On the latest report, negative correlation between miR-145 and NEDD9 was reported to be involved in the regulation of metastasis of PCa [27]. On the other hand, in the TGF-β signal cascade, NEDD9 interacts with Smad3 and is subsequently regulated by proteasomal degradation via ubiquitination by an E3 ubiquitin ligase, atrophin-1-interacting protein 4 (AIP4) [28]. Phosphorylation of NEDD9 on serine/threonine residues by Hesperadin-inhibited kinase (e.g., Aurora-B) triggers NEDD9 degradation by ubiquitin-proteasome system [29]. Further investigations of negative regulation of NEDD9 expression may develop innovative strategies to treat metastatic PCa and to prevent bone metastasis.

In conclusion, NEDD9 is shown to be a fundamental molecule for EMT induced by TGF-β and invasion of PCa. For the PCa patients, NEDD9 may also be a possible marker to predict cancer progressiveness and bone metastasis.

Conflicting interests

The authors have declared that no competing interests exist.

References


