A Role of N-Cadherin in Tumor Progression and Prognosis of Epithelial Malignancy

Harish chandra Rai K, Junaid Ahmed

ABSTRACT

Epithelial cells typically express E-cadherin, mesenchymal cells express various cadherins, including N-cadherin, R-cadherin and cadherin-11. N-cadherin is also known as neural-cadherin, non-epithelial cadherin or cadherin-2 and CD325. The term cadherin switching usually refers to a switch from expression of E-cadherin to expression of N-cadherin. Several studies from current literature have shown de novo expression, re-expression, up-regulation and down-regulation of N-Cadherin in human tumors and tumoral cell lines like breast cancer, gastric cancer, pancreatic cancer, esophageal cancer, oral cancer, prostate cancer, lung cancer, and urinary system cancer. We focus here on the pattern of N-cadherin expression in these malignant tumors of the epithelial origin to evaluate its critical contribution in tumor progression and prognosis.

Keywords: Cancer, Epithelial tumor, N-cadherin, Tumor progression, Cadherin switching.

INTRODUCTION

Cadherins are single pass transmembrane proteins that are synthesized with a single peptide (SP) and pro region (pro), which are removed during protein processing. The extracellular domain comprises five homologous repeats (EC1-EC5) that are bridged by calcium ions (Ca^{2+}). The cytoplasmic domain binds to p120-catenin (p120ctn) near the plasma membrane and α-catenin near the C-terminus. β-catenin binds to α-catenin to link the cadherin complex to the actin cytoskeleton.1

More than 80 different members constitute the group of cadherins, such as the well investigated epithelial, neural and placental cadherins. Epithelial cells typically express E-cadherin, whereas mesenchymal cells express various cadherins, including N-cadherin, R-cadherin and cadherin-11. Endothelial cells express VE-cadherin, which is specific to these cells and is found in the junctional complex, and N-cadherin, which is not found in junctions and has an unclear function. Cadherins are important in the establishment of cell polarity and cell sorting during embryonic development.1,2

N-cadherin was first identified in 1982 (Grunwald et al., 1982) as a 130 kD molecule in the chick neural retina that was protected by calcium from proteolysis, and in 1984 A-CAM was identified (now called N-cadherin) as a molecule that was localised at the adherens junctions (Volk and Geiger, 1984). In the nomenclature of CD antigens the new designation for N-cadherin is CD325, N-cadherin is also known as neural-cadherin, non-epithelial cadherin or cadherin-2. The N-cadherin gene in mice was located on chromosome 18 (Miyatani et al.1989) and via Yeast Artificial Chromosome (YAC) analysis the structure of the human N-cadherin gene was determined, the entire N-cadherin gene was mapped to a 250-kb region on chromosome 18q11.2. The gene is composed of 16 exons, and homology was found not only between human and mouse, but also between N-cadherin and other cadherins (Wallis et al., 1994). N-cadherin typically forms homotypic homophilic interactions; also heterotypic homophilic and heterophilic interactions have been described.3

The term cadherin switching usually refers to a switch from expression of E-cadherin to expression of N-cadherin, but also includes situations in which E-cadherin expression levels do not change significantly but the cells turn on (or increase) expression of N-cadherin. It also includes examples in which other cadherins replace or are co-expressed with E-cadherin, including R-cadherin, cadherin 11, T-cadherin and even P-cadherin, and the expression of the ‘inappropriate cadherin’ might alter the behavior of the tumor cells.1 Several studies from current literature have shown de novo expression, re-expression, up-regulation and down-regulation of N-Cadherin in human tumors and tumoral cell lines. We focus here on the pattern of N-cadherin expression in different malignant tumors of the epithelial origin to evaluate its critical contribution in tumor progression and prognosis.

Breast cancer

In breast cancer, N-cadherin promotes motility, invasion, and metastasis even in the presence of the normally suppressive E-cadherin. The increase in MMP-9 production by N-cad-

1Professor and Head, Department of Oral and Maxillofacial Pathology, KVG Dental College and Hospital Sullia, Professor and Head, 2Department of Oral Medicine and Radiology, Manipal College of Dental Sciences, Mangalore, Manipal University, Karnataka, India.

Corresponding author: Dr Harish chandra Rai K MDS, Professor and Head, Department of Oral and Maxillofacial Pathology, KVG Dental College And Hospital Sullia, Karnataka, India.

How to cite this article: Harish chandra Rai K, Junaid Ahmed. A role of N-cadherin in tumor progression and prognosis of epithelial malignancy. International Journal of Contemporary Medical Research 2016;3(1):77-80.
herin expressing cells in response to a growth factor (FGF-2) may endow them with a greater ability to penetrate matrix protein barriers, while the increase in their adherence to endothelium may improve their ability to enter and exit the vasculature, two properties that may be responsible for metastasis of N-cadherin expressing cells (Rachel B. Hazan and others, 2000).\(^5\) Marvin T. Nieman et al (1999) also suggested that N-cadherin promotes motility and invasion and that decreased expression of E-cadherin does not necessarily correlate with motility or invasion in breast cancer cells.\(^5\)

Overexpression of N-cadherin and Snail were also significantly correlated with poorly differentiated carcinoma, positive node status, and poor Nottingham Prognostic Index. They suggested that increased N-cadherin and decreased E-cadherin expression may be used as indicators of the progression and prognosis of invasive ductal carcinoma (H M Abd ElMoneim et al (2011)).\(^6\) The presence of N-cadherin prevents the re-expression of E-cadherin and localization of β-catenin at the plasma membrane of mesenchymal mammary carcinoma cells. N-cadherin is also required to maintain the expression of VE-cadherin in malignant tumor cells but not vice versa. Thus, N-cadherin acts in concert with VE-cadherin to promote tumor growth.\(^7\) (Maryam Rezaei et al 2012)

Gastric cancer

The abnormal expression of N-cadherin were involved in the process of invasion and metastasis of GC. The data showed that E-cadherin might switch to N-cadherin. TGF-β1 and Snail might play a fundamental role in the process (Yingfeng Zhu et al 2007).\(^8\) Expression of N-cadherin was observed in varying degrees in the intercellular spaces between tumor cells in 11 tubular adenocarcinomas and in six poorly differentiated adenocarcinomas, including E-cadherin-negative cases (Kunio Yanagimoto et al 2001).\(^9\) Takahito Kamikihara et al (2012), also studied the neoexpression of N-cadherin in gastric cancer may be a useful prognostic marker independent of E-cadherin expression.\(^10\)

Pancreatic cancer

N-cadherin expression correlated with neural invasion, histological type, fibroblast growth factor expression in primary tumors and TGF expression and vementin in metatstatic tumors. overexpression of N-cadherin is involved in Epithelial-Mesenchymal Transition (EMT) and is affected by growth factors. Because EMT is an important process in the invasion and metastasis of malignant tumor cells, it is possible that N-cadherin is the adhesion molecule not only to acquire the fibroblastic morphology of EMT but also to obtain invasive and metastatic potential.\(^11\) (S Nakajima et al 2004)

The N-cadherin antagonist ADH-1 has significant antitumor activity against N-cadherin-expressing pancreatic cancer cells, both in vitro and in an orthotopic mouse model for pancreatic cancer (Y Shintani et al, 2008). This study highly implicates N-cadherin as a valid target for treatment of human pancreatic cancer, and suggests that N-cadherin antagonists like ADH-1 that target its adhesive function should be developed for use in treatment of human pancreatic cancer.\(^12\)

Esophageal cancer

N-cadherin expression was negatively correlated to E-cadherin expression in Esophageal squamous cell carcinoma (ESCC). Negativity of E-cadherin and positivity of N-cadherin were correlated to invasion, differentiation, and lymph node metastasis of ESCC. (Ke Li et al 2009)\(^13\) The knock-down of N-cadherin in ESCC cell line (EC9706) could arrest cell cycle at G0/G1 phase, induce cell apoptosis, reduce the invasiveness in vitro, and inhibit the tumor formation in vivo. These results suggest that N-cadherin is an important factor in the progression and metastasis of ESCC and N-cadherin may serve as a potential molecular target for biotherapy of ESCC.\(^14\) (Li K et al 2010).

Oral cancer

The squamous cell carcinoma derived cell line which is expressed N-cadherin and displayed a scattered fibroblastic phenotype along with decreased expression of E- and P-cadherin. Transfection of this cell line with antisense N-cadherin resulted in reversion to a normal appearing squamous epithelial cell with increased E- and P-cadherin expression. In addition, transfection of a normal-appearing squamous epithelial cell line with N-cadherin resulted in downregulation of both E- and P-cadherin and a scattered fibroblastic phenotype.\(^15\) (S Islam et al 1996). Reduced E-cadherin and positive N-cadherin expression are closely associated in oral squamous cell carcinoma, cadherin switching probably plays an a important role in the development of oral squamous cell carcinoma and metastasis.\(^16\) (S W PYO et al 2007)

In oral squamous cell carcinoma, the nuclear pattern of N-Cadherin expression was particularly observed in dedifferentiated cancer, characterized by a worse prognosis (M. Di Domenico et al, 2011). Therefore the pattern of cadherin expression might constitute a useful diagnostic and prognostic tool in the evaluation of tumors and for determining the histogenesis of tumour cells. Moreover, they found a statistically significant correlation between N-Cadherin expression and grade, and a statistical trend for stage.\(^17\)

Nguyen P T et al (2011) suggested that i) N-cadherin may play an important role in malignant behaviors of Head and neck squamous cell carcinoma(HNSCC) and ii) cadherin switching might be considered as a discrete critical event in EMT and metastatic potential of HNSCC.\(^18\) The increased invasiveness seen in N-cadherin expressing cells of the oral squamous cell carcinoma are the result of N-cadherin-driven signaling pathways and not due to the associated loss of E-cadherin (K R. Lawson et al 2006).\(^19\) The upregulation of Snail and N-cadherin and downregulation of E-cadherin correlated significantly with both integrin-linked kinase (ILK) over expression and tumor metastasis (Dan Zhao et al 2012).They suggested that ILK may have an important role in progression and metastasis of oral squamous cell carcinoma, possibly through EMT involving up-regulation of
Snail and consequent aberrant expression of E-cadherin and N-cadherin.\textsuperscript{20}

Prostate cancer
N-cadherin may involved in the progression of prostate carcinoma from epithelium to mesenchyme; it is likely that N-cadherin mediates a less stable cell-cell adhesion and may allow for carcinoma cell invasion and stromal interactions.

N-cadherin mediates adhesion between α-catenin-deficient PC-3N (Prostate cancer) cells and stromal fibroblasts, which contain normal levels of all of the catenins. N-cadherin in PC-3N cells may regulate the cellular outgrowth through cell-cell interactions, which may allow PC-3N to interact with surrounding prostate stromal fibroblasts.\textsuperscript{21} (N L Tran et al 1999).

Meena Jaggi et al (2005), were demonstrated for the first time that N-cadherin switching occurs in higher grade prostate cancer and correlates significantly with increasing Gleason patterns.

N-cadherin may be as a useful biomarker of aggressive prostate cancer.\textsuperscript{22} Formation of N-cadherin junctions promotes 3D (3 dimensional) cell migration of prostate cancer cells, and this is partly due to an aberrant regulation of the N-cadherin complex in the absence of α-catenin.\textsuperscript{23} (Y Cui and S Yamada 2013).

Lung cancer
A study on non-small-cell lung cancer (NSCLC) suggested that, the frequency of hypervascular tumours was significantly higher for N-cadherin-positive carcinomas than for N-cadherin-negative carcinomas and the 5-year survival rate of patients with N-cadherin-positive tumours was significantly lower than that of patients with N-cadherin-negative tumours.\textsuperscript{24} (T Nakashima and other’s 2003)

Specific tyrosine kinase inhibitors for epidermal growth factor receptor (EGFR), such as gefitinib, have been effective in some NSCLC (Non-small cell lung cancer) patients and are being used in the clinical setting as pioneer molecularly targeted cancer drugs. However, many patients have not responded to these drugs, and have acquired resistance after long-term treatment. Mai Yamauchi et al (2011) suggested that, N-cadherin maintains the survival of the gefitinib-resistant lung cancer cells via the PI-3 kinase/Akt survival pathway. So N-cadherin is a potential molecular target in the treatment of NSCLC.\textsuperscript{25} Upregulation of N-cadherin in H1650ER (Erlotinib-resistant cell line) cells leads to increased tumor cell migration, invasion and tumorigenic potential. The maintenance of the EMT phenotype in H1650ER cells may be related to the sustained expression of N-cadherin. Therefore, N-cadherin may serve as a promising new target for the treatment of cancers with acquired resistance to EGFR-TKIs (Epidermal growth factor receptor- Tyrosine Kinase Inhibitors. (Xiaoju Zhang et al (2013).\textsuperscript{26}

Urinary system cancer
N-cadherin plays a different role in renal cell carcinoma (RCC) unlike E cadherin and may be associated with the aggressiveness and malignant potential of RCC (Toru Shimazui et al 2005).\textsuperscript{27} Carl Ludwig Behnes et al (2012) were observed the N-cadherin expression in histological subtypes of papillary renal cell carcinoma and N-cadherin represents the first immunohistochemical marker for a clear cut differentiation between papillary RCC type I and type II and could be a target for therapy and diagnostic in the future.\textsuperscript{28} N-cadherin was present at cell-cell borders in the very anaplastic cell lines of human bladder carcinoma, observed by Mialhe A and others (2000) and they were indicated that N-cadherin may participate in intercellular adhesion, while facilitating bladder tumorigenesis.\textsuperscript{29} in bladder cancer, loss or reduced E-cadherin expression has been associated with poor survival, and aberrant expression of N-cadherin has been associated with the invasive phenotype of bladder carcinoma cells. Richard T. Bryan and Chris Tselepisa (2010), were suggested that Cadherin switching is an important process late in the molecular pathogenesis of bladder cancer.\textsuperscript{30}

CONCLUSION
N-cadherin mediates a less stable cell-cell adhesion and may allow for carcinoma cell invasion and stromal interactions. The loss of E-cadherin expression and gain of N-cadherin expression is called cadherin switching, that is seen during epithelial to mesenchymal transition. Cancer cells derived from epithelium inappropriately express N-cadherin, and the up regulation of N-cadherin expression has been shown to promote motility and invasion. So the maximum expression of N-cadherin by epithelial tumor cells results advanced stage of tumor progression and poor prognosis.

REFERENCES
6. Abd ElMoneim HM, Nasser MZ. Expression of e-cadherin, n-cadherin and snail and their correlation with...
A Role of N-Cadherin in Tumor Progression and Prognosis


Source of Support: Nil; Conflict of Interest: None

Submitted: 16-11-2015; Published online: 01-12-2015