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E-cadherin molecular mechanism in prostate cancer

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Abstract

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in men in USA. In the year 2002, according to the health statistics 189,000 men in the United States are expected to be diagnosed with the disease and 30,200 men are expected to die of it. Mortality in prostate carcinoma is associated with metastasis and metastasis in prostate carcinoma is usually associated with perineural invasion, for it is the preferred mechanism of prostate cancer metastasis. Tumor markers are biological molecules that indicate the presence of malignancy. They are potentially useful in cancer screening, aiding diagnosis, assessing prognosis, predicting in advance a likely response to therapy, and monitoring patients before and after diagnosis. E-cadherin is a promising tumor marker for malignancies in lots of cancer types. Also, the cadherin functional implication in tumor malignancy is an exciting research area in tumor biology, and it is expected to give some insights into how tumors acquire an invasive and metastatic phenotype. Therefore, there are many investigations about E-cadherin activity and its future usage in clinics.

Key words: Prostate cancer, tumor markers, e-cadherins, CAMs, catenin

E-cadherinlerin prostat kanserinde moleküler mekanizması

Özet

Prostat kanseri oldukça sık teşhis edilen erkek solid tümörlerindendir. 2002 yılında, sağlık istatistiklerine göre 189,000 kişinin Amerika Birleşik Devletlerinde bu hastalıktan ötürü teşhis edildiği ve 30,200 tanesininde öleceği tahmin edilmektedir. Prostat kanserinde ölüm metastaz ile ilişkili olup, metastaz perinöral invasyon ile ilişkilendirilmektedir. Tümör belirteçleri biyolojik moleküller olup malign durumları ortaya çıkarmaktadır. Özellikle kanser taramalarında tanı ve tedavi açısından potansiyel avantajları söz konusudur. E-cadherin kanser terapilerini takip açısından umut vaadeden bir tümör belirtecidir. Bunun yanı sıra cadherinlerin fonksiyonel tümör oluşumunda araştırılması gündemde olan konulardan bir tanesidir. Özellikle invasiv veya metastatik tümörlerin fenotipik belirlemesinde önem kazanmışlardır. Bundan ötürü e-cadherin aktivitesinin klinik açıdan kullanılabilirliği üzerine birçok araştırma yapılmaktadır.

Anahtar sözcükler: Prostat kanseri, tümör markırlar, e-cadherinler, CAMs, katenin

What is E-cadherin?

The majority of human cancers originates from epithelial cells. Normal epithelia is organized by a number of specific intercellular junctions, including tight junctions, adherens-type junctions and desmosomes, which are intimately interconnected with the actin and intermediate filament cytoskeleton. This

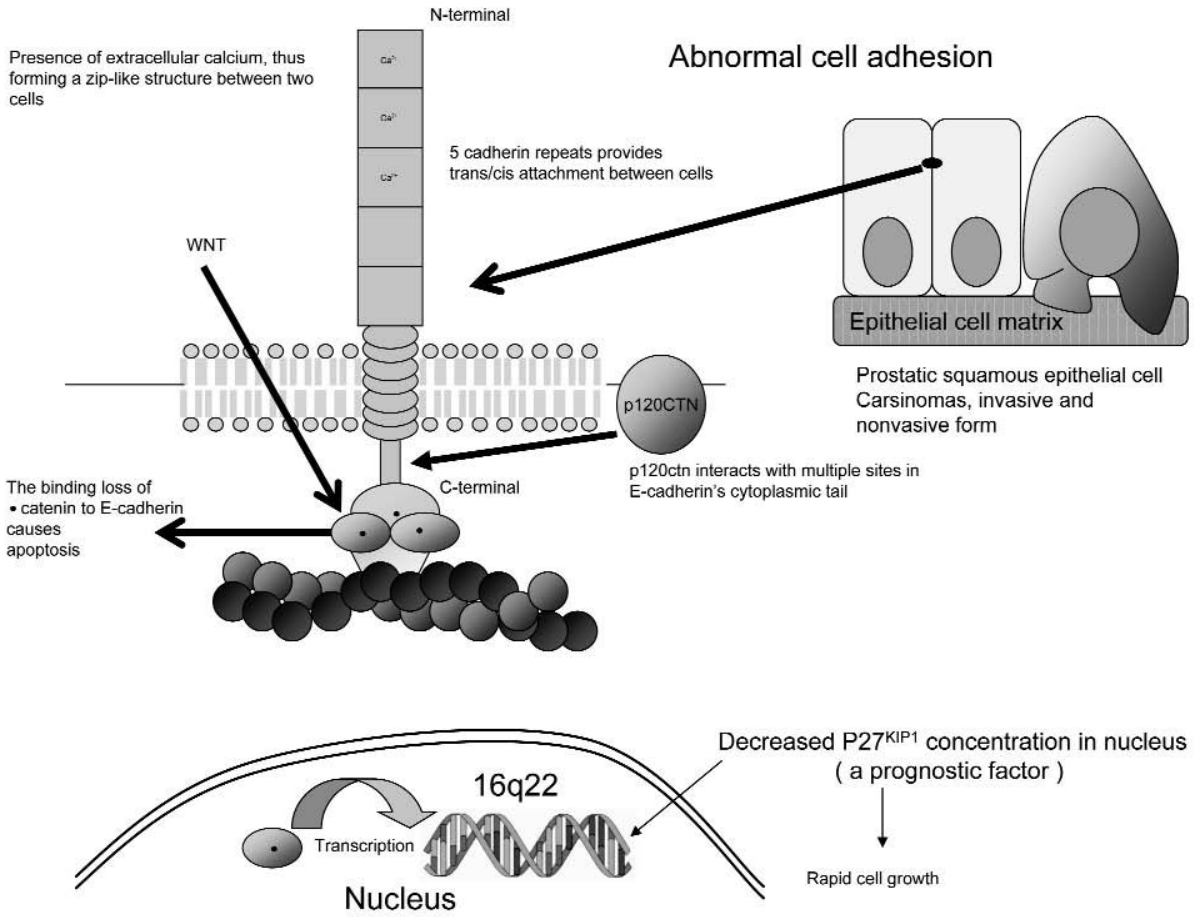


Figure 1: Molecular pathway of E-cadherin molecules in metastatic prostate cells.

association with the cytoskeletal network is necessary for stable cell–cell adhesion and for the integration of cell–cell contacts with the changes in morphology that are characteristic of epithelial cells (e.g. cuboidal cell shape, polarised phenotype). Cell–cell adhesion is an essential component of epithelial morphology and function. Epithelial cells adhere tightly to their neighbours, and several specialised adhesive structures ensure the appropriate integrity and tensile strength of epithelial sheets. Over the past few years, many different laboratories have addressed the questions of how cell-cell adhesion is regulated and how the epithelial phenotype is generated. Although the regulatory processes are not fully understood, several signalling pathways that are activated by cell-cell adhesion have been identified (DeMarzo et al., 1999; Umbas et al., 1997; Behrens, 1999; Takeichi, 1991).

Among the many types of cell-cell adhesion molecules, cadherins play a critical role in establishing adherens-type wuctions by mediating Ca^{2+}-dependent cell-cell adhesion (Takeichi, 1995; Huber et al., 1996; Yagi et al., 2000). Cadherin-based cell-cell adhesion is critically involved in early embryonic morphogenesis, as exemplified by the early embryonic lethality of mice lacking E-cadherin, a prototype classical cadherin (Riethmacher, 1995; Larue et al., 1994). One of the most studied molecules involved in cell-cell adhesion is E-cadherin, a 120 kDa transmembrane glycoprotein. The cytoplasmatic moiety of E-cadherin binds to β- and γ-catenin, which are linked to the cytoskeleton via α-catenin, while the extracellular moiety is a calcium-dependent receptor responsible for homophilic (E-cadherin/E-cadherin) interactions (Takeichi, 1995).

Cadherin-mediated cell-cell adhesion is accomplished by homophilic protein-protein

interactions of extracellular cadherin domains in a zipper-like fashion. The intracellular domain of classical cadherins interacts with various proteins, collectively termed catenins, which assemble the cytoplasmic cell adhesion complex (CCC) that is critical for the formation of extracellular cell-cell adhesion. β-catenin and γ-catenin (also called plakoglobin) bind to the same conserved site at E-cadherin's C-terminus in a mutually exclusive way (Nathke et al., 1994; Ozawa et al., 1984; Witcher et al., 1996), whereas p120ctn interacts with multiple sites in E-cadherin's cytoplasmic tail, including its juxtamembrane region (Yap et al., 1998; Ozawa, 1998). β-catenin and γ-catenin bind directly to α-catenin, which links the CCC to the actin cytoskeleton. While the dual role of β-catenin and γ-catenin in cell adhesion and Wnt-signaling has been extensively studied, the functions of p120ctn are poorly understood. p120ctn has been implicated both in cell-cell adhesion and in cell migration (Anastasiadis and Reynolds, 2000), and recent studies suggest that p120ctn promotes cell migration by recruiting and activating Rho-family GTPases (Noren et al., 2000) (Figure 1).

Why prostate cancer is too important

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in men in USA. In the year 2002, according to the health statistics 189,000 men in the United States are expected to be diagnosed with the disease and 30,200 men are expected to die of it. Incidence varies greatly, with African Americans having the highest incidence in the world (224 cases per 100,000 population). The incidence of prostate cancer in African Americans stands in stark contrast to the incidence in white Americans (150 per 100,000) and that in men in Western Europe (39.6 per 100,000), Japan (8.5 per 100,000), and China (1.1 per 100,000) (American cancer soc. reports, 2002; Robbins et al., 1998). Mortality in prostate carcinoma is associated with metastasis and metastasis in prostate carcinoma is usually associated with perineural invasion, for it is the preferred mechanism of prostate cancer metastasis. One of the current theory states this form of metastasis follows the path of least resistance offered by the perineural sheath. Understanding specific mechanisms of this carcinoma/nerve interaction is key to potential therapeutics targeted to this process. Death from prostate cancer is the result of metastasis and local spread, not from organ-confined disease. Hence, understanding the mechanism of prostate cancer spread and metastasis is the key to treating this disease successfully and increasing survivability (Jiang et al., 1994).

Tumor markers are biological molecules that indicate the presence of malignancy. They are potentially useful in cancer screening, aiding diagnosis, assessing prognosis, predicting in advance a likely response to therapy, and monitoring patients before and after diagnosis (Mason et al., 2002; Tomita et al., 2000). Because of low prevalance of most cancers in the general population and the limited sensivity and spesificity of avaible markers, these tests alone are generally of little value in screening for cancer in healthy subjects. Currently, however, prostate spesific antigen (PSA) in combination with digital rectal examination (DRE) are undergoing evaluation as screening modalities and case findings for prostate cancer (Mettlin et al., 1994). Because of a lack of sensitivity and spesificity markers are rarely of use in early diagnosis of cancer. Also they can be used to monitor the disease during therapy. The goal of future research should be to develop the most specific, cheap and easy markers for common cancer types as prostate cancer (Arisan, 2003).

The natural history of prognostic factors involved in prostate cancer are not clearly defined. Hence, molecular parameters that are able to accurately assess the aggressiveness and the metastatic potential of the cancer are urgently needed (Arisan, 2003, Gao et al., 1997; Pettaway, 1998). Since vascular invasion and the spread of prostate tumor cells to the blood represent preliminary steps in the metastatic process, blood-borne detection of circulating prostate epithelial cells (CPC) could be an early marker of invasiveness (Gomella et al., 1997). The recent development of sensitive molecular techniques evidenced such cells in the blood and urine of patients with localised prostate cancer, and has been proposed as a new staging modality. One of the prominent features of the development and progression of prostate cancer is the development of abnormalities in cell adhesion in prostate epithelium and prostate cancer cells. These abnormalities extend to intercellular adhesion structures and cell–matrix adhesion molecules.

The metastatic process consists of a complex pattern of sequential steps whose primary event requires the detachement of cells from the primary tumor. The metastatic cascade is composed of a

number of separate but important steps, including cell adhesion ability decreament. Disruption of normal cell-cell adhesion in transformed cells contributes directly to tumor cells' enhanced migration and proliferation, leading to invasion and metastasis. Most prostate cancer deaths are due to metastatic disease, but it is not significant means to combat metastasis in prostate cancer (Vleminckx et al., 1991; Birchmeier and Behrens et al., 1999).

Is e-cadherin a tumor supressor gene?

The concept of the tumor suppressor gene has been extended to genes which are subject to frequent downregulation in cancer, suggestive of an important tumor-suppressing activity despite the lack of evidence for mutation. Examples include cell adhesion molecules (CAMs) which play important roles in tissue development and epithelial cell differentiation. When downregulated, CAMs may be involved in oncogenic processes through inactivation of cell adhesion-mediated growth control pathways. E-cadherin is a member of a family of Ca^{2+} dependent homophilic CAMs involved in developmental morphogenesis and maintenance of the epithelial phenotype (Tomita et al., 2000). E-cadherin expression correlates with epithelial differentiation whereas loss of E-cadherin expression promotes epithelial dedifferentiation and invasiveness of human carcinoma cells. Restoration of wild-type E-cadherin function prevents invasiveness of epithelial tumor cells (Hatta and Takeichi, 1986). Absence of E-cadherin immunostaining has been shown in many carcinoma types including mouse squamous cell carcinoma of the skin, human infiltrating basal cell carcinoma, head and neck, breast, colorectal, gastric, and other carcinomas (Edelman et al., 1983). Loss of expression of E-cadherin which is located on chromosome band 16q22 may be associated with a biallelic mutation mechanism characteristic of tumor suppressor gene inactivation. Potentially inactivating point mutations of E-cadherin associated with LOH have been identified in gastric cancer cell lines derived from signet ring and diffuse stomach cancers, both of which are poorly differentiated forms of gastric carcinoma (Doherty and Walsh, 1996). DNA methylation in mammalian cells occurs at the 5-position of cytosine within the CpG dinucleotide. This reaction is catalysed by the DNA methyltransferase (DNMT) enzymes. More in general, DNA methylation often causes the downregulation of tumor suppressor genes (such as pRb, p15 INK4a, p16INK4a) in cancer cells by changing chromatin structure, thereby making the DNA inaccessible for transcription factors and RNA polymerase II. Also, downregulation of E-cadherin expression is often accompanied by methylation of 5' CpG island of E-cadherin in lung, liver, bladder and gastric carcinoma cell lines. The picture that emerges from the analysis of all of these studies suggests that promoter hypermethylation is the main mechanism involved in promoter silencing of E-cadherin in those tumors, although not the only one. The data presented in the two papers confirm that loss of heterozygosity (LOH) and/or point mutation (or even other mechanisms) also contributes to the downregulation of E-cadherin. The mechanistic question remains as to whether aberrant promoter methylation in those tumors is a causal and not consequent to malignant transformation. Future studies, probably investigating the status of E-cadherin promoter methylation at different stages (e.g. premalignant versus malignant lesions) might help in addressing this question (Bird, 2002, Di Croce et al, 2002, Robertson, 2002, Tsao et al., 2003; Chen et al., 2003).

Further suggestions of the mechanisms by which E-cadherin is inactivated in cancer are analogous to those observed for classical tumor suppressor genes. The role of E-cadherin in prostate cancer was initially investigated in the Dunning R-3327 rat prostatic cell line. E-cadherin mRNA and protein expression was found in well and poorly differentiated lines with low invasive potential, while all established cell lines with high invasive potential had no detectable levels of E-cadherin mRNA (El-Hariry et al., 2001). In human prostate cancer, E-cadherin immunostaining was reduced or absent in 46 of 92 primary and metastatic cases whereas benign non-malignant tissue stained uniformily positive (De Luca et al., 1999).

E-cadherin molecular mechanism in cancer

It has long been known that cell-cell adhesion is dramatically changed during the development of malignant tumors. In particular, in most if not all cancers of epithelial origin, E-cadherin-mediated cell-cell adhesion is lost concomitant with progression towards malignancy, and it has been proposed that the loss of E-cadherin-mediated cell-cell adhesion is a

prerequisite for tumor cell invasion and metastasis formation (Birchmeier and Behrens, 1994). Multiple mechanisms are found to underlie the loss of E-cadherin function during tumorigenesis: mutations or deletions of the E-cadherin gene itself, mutations in the β-catenin gene, transcriptional repression of the E-cadherin gene, for example by hypermethylation or chromatin rearrangements in the E-cadherin promoter region and, finally, aberrant tyrosine phosphorylation of the components of the CCC (Hirohashi, 1998). Recent reports have highlighted that the DNA binding protein Snail acts as a strong repressor of E-cadherin gene expression in tumor cells, thus inducing tumor malignancy (Batlle et al., 2000, Cano et al., 2000, Poser et al., 2001; Yokoyama et al., 2001).

The observation that E-cadherin function is frequently lost in malignant tumors prompted an examination of the functional role of E-cadherin in tumor progression. Using tumor cell lines in culture, several groups demonstrated that re-establishing the functional cadherin complex, for example by forced expression of E-cadherin, resulted in a reversion from an invasive to a benign, epithelial tumor cell phenotype (Birchmeier and Behrens, 1994, Hirohashi, 1998, Battle et al., 2000, Cano et al., 2000, Poser et al., 2001, Yokoyama et al., 2001; Vleminckx et al., 1991). Although these experiments clearly demonstrated a critical role for E-cadherin in the suppression of tumor invasion in cultured cells, it remained elusive whether the loss of E-cadherin mediated cell adhesion is a pre-requisite for tumor progression or whether it is instead a consequence of de-differentiation during tumor progression. It is recently shown that expression of E-cadherin is lost during the transition from well-differentiated adenoma to invasive carcinoma in a transgenic mouse model of pancreatic β-cell tumorigenesis (RIP1TAG2). Maintenance of E-cadherin expression during β-cell tumorigenesis resulted in arrest of tumor development at the adenoma stage. By contrast, expression of a dominant negative E-cadherin induced early invasion and metastasis. These results demonstrate that loss of E-cadherin-mediated cell-cell adhesion is one the rate-limiting steps in the progression from adenoma to carcinoma in vivo and highlight the role of E-cadherin as a suppressor of tumor invasion. However, several questions remain to be answered. Tumor invasion is the result of a sequence of multiple cellular events, involving not only changes in cell-cell adhesion but also in cell-matrix adhesion, cell migration, proteolytic degradation of extracellular matrix and so forth. Therefore, it is difficult to envisage that the loss of E-cadherin-mediated cell adhesion per se is sufficient to confer an invasive phenotype to tumor cells. It seems more likely that E-cadherin downregulation results in the activation of specific signaling pathways which, in turn, trigger tumor cell invasion. One of the obvious candidates for activating such signaling pathways is β-catenin. Besides being a component of the CCC, β-catenin plays a key role in Wnt-mediated signal transduction. β-catenin is usually sequestered in the E-cadherin adherens junction or in tight-junction complexes. Non-sequestered, free β-catenin is rapidly phosphorylated by glycogen synthase kinase 3b (GSK-3b) in the adenomatous polyposis coli (APC)/GSK-3b/axin complex and subsequently degraded by the ubiquitin-proteasome pathway. If the tumor suppressor APC is non-functional, as is the case in many colon-cancer cells, or GSK-3b activity is blocked by activated Wnt signaling, β-catenin accumulates at high levels in the cytoplasm. Subsequently, it translocates to the nucleus, where it binds to a member of the TCF/LEF-1 family of transcription factors and modulates expression of TCF/LEF-1-target genes. Target genes of TCF/β catenin that could be relevant for tumor progression include the proto-oncogene c-Myc and cyclin D1 (Perl et al., 1998, Bienz and Clevers, 2000; Polakis, 2000). Future investigation should focus on the relationship between E-cadherin downregulation and β-catenin signaling during tumor progression, in particular addressing the issue of whether the loss of E-cadherin results in the activation of the Wnt signaling pathway thus endowing tumor cells with an invasive phenotype. Not much attention has been devoted to the role of the cytoskeleton upon the loss of E-cadherin-mediated cell-cell adhesion and the induction of tumor malignancy. Cadherin-based adhesion complexes are functionally linked to the dynamics of actin and microtubule cytoskeletal structures (Vasioukhin and Fuchs, 2001; Chausovsky, 2000). Thus, it can be anticipated that the loss of E-cadherin mediated cell adhesion leads to dramatic cytoskeletal rearrangements. Cellular factors that connect cadherin function with cytoskeletal organization are likely to play a key role in the structural alterations following the downregulation of cadherin-mediated cell adhesion. Small GTPases of the Rho family are obvious candidates for future investigation, since besides controlling the actin cytoskeleton they are known to modulate cadherin activity (Braga, 2000, Kaibuchi et

al., 1999; Gumbiner, 2000). Interestingly, among the molecules linking small GTPases with cadherin function is IQGAP1, a protein whose dysregulation has been proposed to correlate with malignancy in gastric cancer (Takemoto et al., 2001; Sugimoto et al., 2001).

In conclusion, the cadherin switch and its functional implication in tumor malignancy is an exciting research area in tumor biology, and it is expected to give some insights into how tumors acquire an invasive and metastatic phenotype. However, several issues need to be addressed before considering the cadherin switch as a crucial step in tumor progression. Thus far, the cadherin switch *in vivo* has only been described during the development of malignant melanoma and prostate carcinoma. Further studies on other tumor types are required to establish whether a switch in cadherin expression is a common mechanism underlying tumor progression. *In vitro* observations on various tumor cell lines suggest that this might indeed be the case. In addition, although the classical cadherin family comprises at least 30 members, not many attempts have been made to investigate the expression of cadherins other than E- or N-cadherin in different tumor types. Such systematic studies might provide evidence of tumor specific cadherin repertoires, thus raising the possibility that many more members of the cadherin family are involved in cadherin switches and that the cadherins involved in the switch vary in a tumor-specific manner. Forced expression or genetic ablation of particular cadherin genes during embryonic development or in appropriate mouse models of tumorigenesisesis or other disease will help in unraveling the functional role of the cadherin switch (es) in physiological and pathological processes. Extensive investigations on the functional relevance of the cadherin switch *in vivo* may not only provide additional insights into the molecular mechanisms underlying tumor progression, but may also allow the identification of novel molecular targets for anti-cancer therapy.

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