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REVIEW ARTICLE

EpCAM- AN OLD CANCER ANTIGEN, TURNED ONCOGENIC RECEPTOR AND ITS TARGETING IMMUNOTHERAPY

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ABSTRACT
EpCAM is a cell adhesion molecule. Its structure, its expression and the oncogenic potential, and its signaling network and target therapy were in concise reviewed. In recent advances, in addition to PI3K/akt and Raf/MAPK pathway involving in cell survival, anti-apoptosis and proliferation,and malignant initiation and progression, three distinct pathway are illustrated: EpCAM/E-cadherin-catenin-actin cytoskeleton, EpCAM/wint-catenin signaling and its major EpCAM/nuclear signaling presented by Maetzel D in 2009 and Munz M in 2004. Moreover, more accumulated data are needed in detail mechanism. The data may provide its cancer biology and clinical targeting therapy benefits.
Keywords: EpCAM, nuclear signaling, structure, target therapy.

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INTRODUCTION
In a series of long list of oncogenic receptors which discriminated tumorigenic in partial origin of tumors from receptors in normal health people and then better to potential targeting therapy benefits are presented in clear in previous references (Table 1)[1-6]. Because It is no need to targeting receptors in normal condition, actually, targeting therapy now is shift mainly toward oncogenic receptors in tumours in tumor hospitals, even if we won't citing in literature[7]. EpCAM molecule a novel oncogenic receptor is shift toward new member family and targeting its antibodies[34]. In this article recent advances on EpCAM in this field are deliberated. The epithelial cell adhesion molecule [EpCAM] was originally identified as a tumor associated antigen in discovery in 1970s[36], also known as cluster of differentiation 326（CD326, and tumor-associated calcium signal transducer 1（TACSTD1)[37]. EpCAM is a type I transmembrane protein of 314 amino acids (aa)with apparent molecular weight of 40KD. The extracellular domain(EpEX)contain epidermal growth factor-like domain, a thyroglobin（TY) repeat domain, tansmembrane domain（TM) and a short 26-amino acid intracellular domain（EpICD（Figure 1)[34-37]. EpCAM is an oncogenic receptor that requires regulated intramembrane proteolysis for activation of its signal transduction capacity[34]. EpCAM cleavage is dependent on cell-to-cell contact. Thus, EpCAM as an oncogenic signaling protein engaged in cell adhesion and nuclear signaling[37-38].

EpCAM expression, a dual player
EpCAM is expressed by the epithelium of health individuals（all simple, pseudo-stratified and transitional epithelia), except by squamous epithelium, and some specific epithelial cell types, such as hepatocytes and keratinocytes[39]. EpCAM is a membrane protein with proto-oncogenic properties that is expressed in most human carcinomas, EpCAM is over expressed to varying degrees[40]. These include the majority of adenocarcinomas including pancreatic adenocarcinoma, cholangiocarcinoma, node-positive breast cancer, epithelial ovarian cancer, lung cancer, colon carcinoma, prostate cancer, gastric cancer, hepatic carcinoma and squamous cell head and neck cancer[41-43]. Recently, EpCAM has been identified as an additional marker for cancer-initiating stem cells[44-46]. The oncogenic potential of EpCAM or EpICD was demonstrated in a mouse xenograft model, in which HEK 293 cells stably expressing EpCAM or EpICD produced nearly equivalent large tumours,whereas control cells only formed a small tumour in a single case[38]. EpCAM expressing pancreatic cancer stem cells showed a 100-fold enhanced tumorigenic potential

compared with EpCAM-negative pancreatic cancer stem cells[47,48]. Similarly, *in vivo* evaluation of tumorigenicity in hepatocellular carcinoma cell lines, using immune deficient NOG mice, a smaller number of EpCAM$^+$ cells（minimum 100）than EpCAM- cells are able to tumor formation. The introduction of exogenous EpCAM into EpCAM$^+$ clones,but not into EpCAM- clones, markedly enhanced their tumor-forming ability[45]. Also, EpCAM-positive hepatocellular carcinoma stem cells could efficiently initiate tumours in SCID mice[46]. Very recent, EpCAM-proliferating ductal cells（PDC）give rise to hepatocellular carcinoma（HCC）in the inflamed liver[48], which provide direct experimental evidence that EpCAM expressing PDC could be a cellular origin of HCC, suggesting the existence of stem/progenitor-derived hepatocarcinogenesis. For breast cancer stem cells, the ability to form tumours in SCID mice was for EpCAM$^+$ cells 50-fold greater compared with the unfractioned tumour cells[47]. Therefore, although EpCAM- and EpCAM$^+$ cancer stem cells were able to form tumours, 10-fold less EpCAM$^+$ cells than EpCAM- cells were able to induce tumours. Indeed, EpCAM over expression is associated with decreased overall survival of patients with a broad variety of carcinoma[42,47].

In contrast to its promoting role regarding tumour formation, high EpCAM expression only in two tumour types（renal clear cell carcinoma and thyroid carcinoma）has been consistently associated with improved patient survival[47,49].

Table 1: Receptors with oncogenic potential associated with tumours(also receptor-mediated tumorigenesis)

Growth factors receptors:	Oncogenic receptor EGFRvIII (GB, MLC, SCC[8-11], Oncogenic receptor MUC1[12] or MUC4[12], Neu oncogenic receptor (breast cancer)[13] ; Oncogenic receptor IGF-1R[14]; Oncogenic B receptor (HCD, CLL)[14] and other VEGFR2(colorectal cancer, glioma)[2829]
Cytokine receptors	Oncogenic growth hormone receptor（gigantism, acromegaly)[15]; GHRH/GHRHR oncogenic signaling（pituitary tumors); Oncogenic EPOR(PFCP)[16], oncogenic EPOR-IGH/IGK fusion（BCP-ALL)[17]; Oncogenic CSF3R（CNL or aCML)[18]; IL-2-BCM fusion（T cell lymphoma); IL-3-IgH oncogenic fusion (ALL); IL-11/IL-11 receptor（gp130 Y757F/Y757F）pro-oncogenic signaling（gastric tumor in mice)[19,20]; IL-21R-BCL6 fusion（DLBCL, lymphoma cell line; Oncogenic TSHR（thyroid adenoma）
Steroid receptors	Oncogenic thyroid hormone receptor (TR）(PTC)[21],oncogenic THR1/BTR fusion（breast cancer cell line; oncogenic receptor pml/RARa (APL)[22,23]; Oncogenic receptor AR variants（Pca)[24-25]; ER pro-neoplastic signaling[26-27], neoplastic ESR1-CCDC170 fusion (also oncogenic receptor ERalpha fusion)（breast cancer)[7,28];GRβ aberrant signaling (Cushing's disease, erythrocytosis, GR$^+$ breast cancer, Nelson's syndrome)[29-31]; FSH/FSH receptor oncogenic signaling (preneoplastic ovarian surface epithelial cells)
Others	Pro-oncogenic receptor CLC1[32]
Tobacco related cancer（toxicology）	nicotinic acetylcholine receptor alpha7-nAchR oncogenic receptor[33]

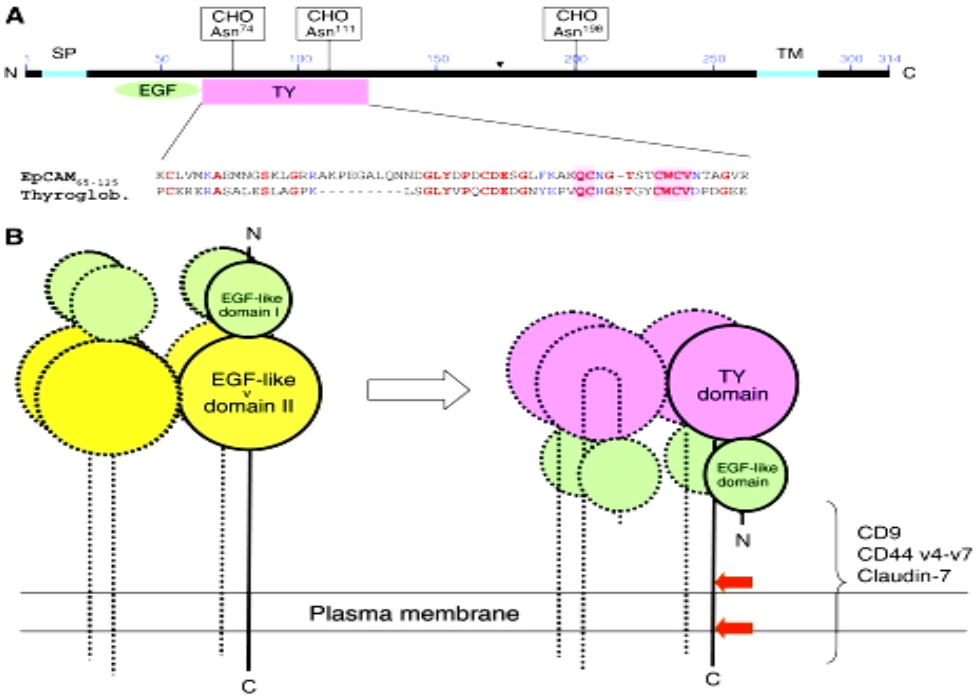

Figure 1: EpCAM structure[37]

Signal transduction by EpCAM oncogenic receptor and its target pathway

Several biological function of EpCAM has been described. EpCAM is a cell adhesion molecule, its action was invented in fact, is not limited on adhesion between cell and cell and also can activate intracellular MAPK and PI3K/Akt signal to cause tumor cell proliferation invasion and metastasis etc. biological action（Figure 2, George Zhu,1991; Hu *et al.*, [1]) Recent advances further uncovers a highlight of new data in its distinct signal pathway.

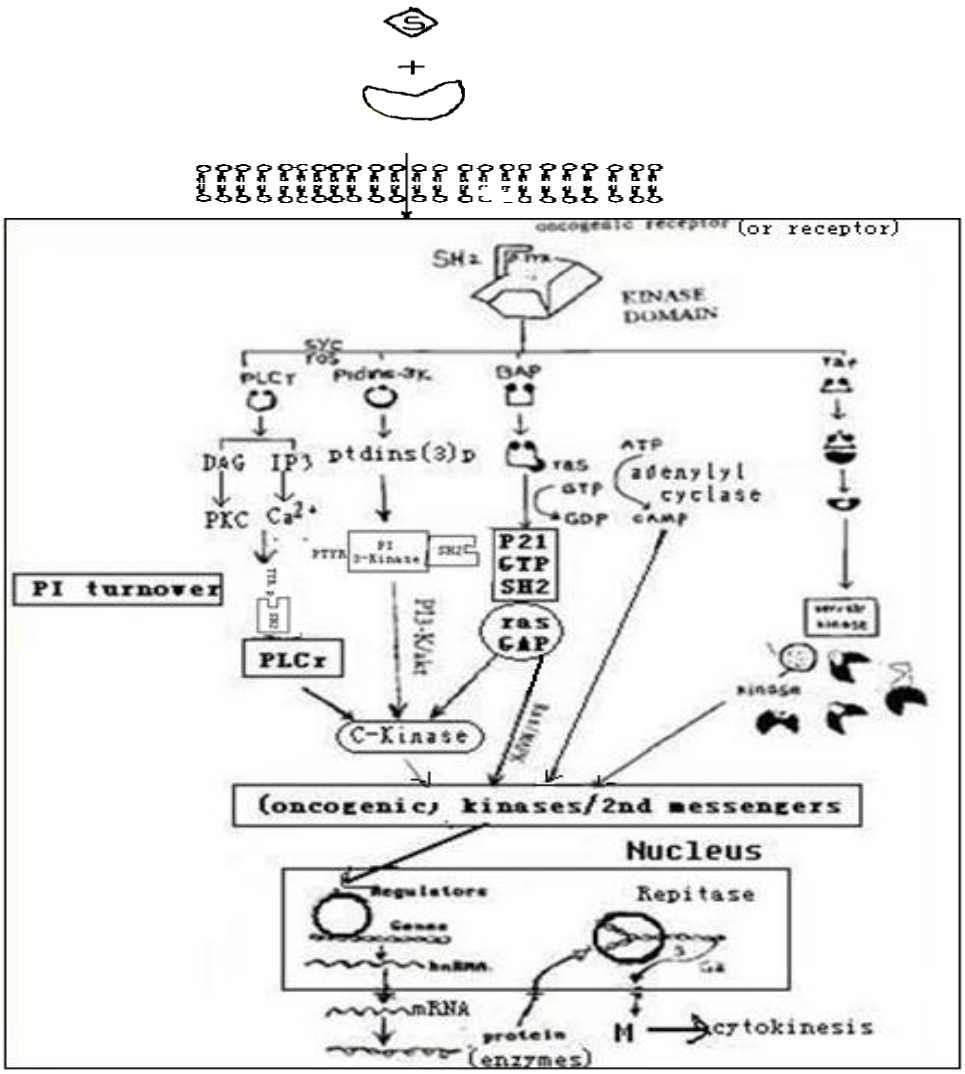

Figure 2: A Scheme of oncogenic receptor (or receptor) mediated multiple signal transduction.

(Here, nuclear regulators include transcriptional factors such as Jun/AP-1: Fos, NF-KB,myc, p53 and RB so on)

[Data from George Zhu[1], 1991; Science, 2002 (unpublished data)]

EpCAM/E-cadherin-catenin-actin cytoskeleton (E-cadherin-mediated adhesion）

Adhesion molecules are known to play an important role in definiting cell fate, differentiation and other biological characteristics[50]. EpCAM is a Ca^{2+}-independent homotypic intercellular adhesion molecule[35], thereby preventing cell scattering and likely to play a role in inhibition of invasion[51]. Many studies have demonstrated that cadherin colocalized with EpCAM at the basolateral membrane in epithelial cells decrease adhesions mediated by E-cadherin, a family of Ca^{2+}-dependent homophilic cell-to-cell adhesion molecule. In epithelia cadherins are crucial for the establishment and maintenance of epithelial cell polarity, morphogenesis of epithelial tissues and regulation of cell proliferation and apoptosis[50].

Furthermore the adhesion function of E-cadherin depends on their association with regulatory proteins such as alpha- and beta-catenin[50,52]. Catenins link cadherins with the actin cytoskeleton and can also form complexes with other epidermal growth factor receptor（EGFR）protein[52,53]. EpCAM is able to abrogate E-cadherin- mediated cell-cell adhesion by disrupting the link between alpha-catenin and F-actin thereby loosening cell-cell adhesion and to rearrange the cytoskeleton of the cell[39]. This negative effect of EpCAM expression on cadherin-mediated adhesion may explain the association of EpCAM expression with invasion and metastasis in epithelial carcinoma[41]. EpCAM SiRNA treatment increased the cytoskeleton-anchored fractions of E-cadherin alpha-catenin and beta-catenin, then markedly decreased cell migration

and cell invasion in the breast cancer cell line MDA-MB-231 *in-vitro*[41], which implicated that EpCAM as a regulator of cell adhesion is a potential novel target for breast cancer therapy.

EpCAM/wnt-beta-catenin signaling

Wnt proteins are a family of highly conserved signaling molecules that regulate cell-to-cell interaction during embryogenesis[41,54]. Wnt binds to receptors of the Frizzled family on the surface. Through several cytoplasmic relay components, the signal is transduced to beta-catenin, which accumulates initially in the cytoplasm, and then enters the nucleus where it binds a lymphoid enhancer factor/T-cell factor transcriptional factor. The beta-catenin and lymphoid enhancer factor/T-cell factor complexes activate the expression of many target genes such as c-myc, VEGF and others, are known to be associated with tumor development[54]. It has been demonstrated that EpCAM silencing in breast cancer cells decreased the availability of beta-catenin for the wnt pathway and then silencing the activation of its target genes[41].This notion is also supported by Yamashita in patients with hepatocellular carcinoma and Kimura[45-46] in hepatocellular carcinoma cell lines.Their experiments uncovered that EpCAM-associated tumorigenicity in PLC/PRF/5 cells might be mediated by EpCAM-independent signaling due to the immunostaining failed to detect EpICD and EpCAM molecules in the nuclei of any cell clones from the PLC/PRF/5 cell lines. Moreover, the hepatic stem cell marker EpCAM knockdown in $EpCAM^+$ cells reduces their colony-forming ability suggesting an important role for EpCAM in the $EpCAM^+$ cells and regardless of the exogenous expreasion of EpCAM, $EpCAM^+$ clones still had higher expression of c-myc, than the EpCAM-over expressing EpCAM- clones. Therefore signals through EpCAM induce Wnt/beta-catenin activation might be involved to another different signaling pathway in tumorigenesis under certain condition[45-46].

EpCAM nuclear signaling

A highlight of new data presented by M. Munz that unravelled the entire pathway of EpCAM signalling from the cell membrane into nucleus[55]. EpCAM was identified as a signal transducer[38]: regulated transmembrane proteolysis by tumor necrosis factor-alpha-converting enzyme（TACE）cleaves EpEX and EpICD is cleaved by presenilin-2. Upon cleavage the extracellular domain EpEX is release as a soluble ligand while the intracellular domain EpICD translocates into the cytoplasm and enter the nucleus. EpICD associates with the adaptor protein FHL2（four and a half LIM domain protein 2, beta-catenin and the transcription factor Lef-1. This transcription complex binds the DNA at the lef-1 consensus sites inducing target genes c-myc and cyclin A and E expression[38], and drives cell proliferation. This notion is supported by the EpCAM found in nuclei of colon carcinoma but not of normal tissue[38], and HCT（colon）and MCF-7（breast）carcinoma cells[34]. In addition, analysis for concomitant presence of claudin 7, Co-029, CD44V6 and EpCAM expression in the presence of all four molecules in a complex formation was initially found in colorectal cancer (CRR) and has been shown to facilitate metastasis[56].

Others, epithelial-specific Ets-1 and Sp1 play an active role in EpCAM promoter regulation[37], while transcription factor nuclear factor-kappa B（NF-KB）and p53 have been described as transcriptional repressor of EpCAM[47]. TACE-dependent EGFR axis[57], Claudin-7 and claudin-1 trafficked into lysosomes[58] and presenillins mediate PI3K/akt and ERK activation via select signaling receptors[59],which present a highlight mechanism in cancer. The emerging function of EpCAM in cell proliferation, migration and possibly cancer initiation broadens the interest to use EpCAM as an immune target, antibody-based clinical trials and in 2009, the European Medicines Agency approved the use of tri functional bi specific antibody Catumaxomab, which binds to EpCAM oncogenic receptor and enhances the immunological response against EpCAM-positive cells in malignant ascites[43]. Effects of monoclonal antibody immunotherapy was initially trials on patients with gastrointestinal adenocarcinoma[60], three of 20 patients with metastasis of gastrointestinal malignancies have no detectable disease for 10,13 and 22 months due to the treatment with an anti-colorectal cancer mouse monoclonal antibody 1083-17-1A of the IgG2a immunotherapy. In 1989-91, Zhu[1] is the first to conduct that targeting therapy is shift toward oncogenic receptor [also surface-to-nucleus molecular missile therapy at that period, Zhu, 1980s[34,61]. In 1994, mAb17-1A（later named edrecolomab）was also the first to show clinical efficacy in a human cancer indication in terms of prolonged overall survival[62]. Now, several anti-EpCAM therapeutic antibodies have been developed (edrecolomab, ING-1, 3622W94, adecatumumab[63]. The most prominent example is adecatumumab (MT201, a fully human IgG1 antibody that target oncogenic EpCAM, which was well tolerated by patients with hormone-refractory prostate cancer and in patients with rising prostate specific antigen (PSA）levels after radical prostatectomy[43]. It is at present reaching phase III trial[64]. In preclinical study, moreover, high doses of chiHEA125-Ama (100μg/Kg with respect to alpha-amanitin）administered 1 week apart, lead to complete tumor regression in 9 of 10 (90%）mice, suggesting that anti-EpCAM antibody conjugates with alpha-amanitin have the potential to be highly effective therapeutic agents for pancreatic carcinoma and various EpCAM-expressing malignancies. Targeting EpCAM oncogenic receptor might be a promising approach to stop tumor initiation, invasion and progression.

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