EpCAM, a novel oncogenic receptor and its target therapy

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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. EpCAM is expressed in a broad variety of human carcinomas to varying degrees. The identification of EpCAM describing both a protective and a promoting role in carcinogenesis appears to be dependent on the cancer type. 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. Indeed, the use of the EpCAM-specific monoclonal antibody has been successful in increasing disease-free survival in colon and breast cancer patients with minimal residual disease.

Introduction

In a series of long list of oncogenic receptors which discriminated tumorigenic in partial origin of tumours from receptors in normal health people and then better to potential targeting therapy benefits are presented in clear in previous references [1-7]. Because It is no need to targeting receptors in normal condition, at present, targeting therapy[8-10] is shift mainly toward oncogenic receptors in tumours in tumor hospitals, even if we won’t citing in literature (Figure 1, Table 1).

EpCAM molecule, a novel oncogenic receptor [65] is shift toward new member family and targeting its antibodies. In this paper, I am deliberating recent advances on EpCAM in this field.

EpCAM structure

The epithelial cell adhesion molecule [EpCAM], [66-67] was originally identified as a tumor associated antigen in discovery in 1970s [68], also known as cluster of differentiation 326 (CD326), and tumor-associated calcium signal transducer 1 (TACSTD1) [69]. EpCAM is a type I transmembrane protein of 314 amino acids (aa) with apparent molecular weight of 40kd [70]. The extracellular domain (EpEX) contain epidermal growth factor-like domain, a thyroglobulin (TY) repeat domain, transmembrane domain (TM), and a short 26-amino acid intracellular domain (EpICD) (Figure 1) [65,69-70]. It is encoded by the GA733-2 gene located on the long arm of chromosome 4 [71].

EpCAM is an oncogenic receptor [65] that requires regulated intramembrane proteolysis for activation of its signal transduction capacity. EpCAM cleavage is dependent on cell-to-cell contact. Thus, EpCAM as an oncogenic signaling protein [69] engaged in cell adhesion and nuclear signaling [72].

EpCAM expression, a dual player

EpCAM is expressed by the epithelium of health individuals (all simple, pseudo-stratified and transitional epithelia, with the exception of the adult squamous epithelium, and some specific epithelial cell types, such as hepatocytes, keratinocytes, gastric parietal cells, myoepithelial cells and thymic cortical epithelium. However, de novo expression of EpCAM can be observed for these cell types as well during active cell proliferation, whether normal or neoplastic [73]. EpCAM is a membrane protein with proto-oncogenic properties that is expressed in most human carcinomas. EpCAM is overexpressed to varying degrees [74]. 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 [74-76]. Using RT-PCR, EpCAM is approximately 100-fold to 810-fold higher in primary and metastatic breast cancers than in normal breast tissues. EpCAM SiRNA treatment decreased cell migration by 91.8% and cell invasion by 96.4% in breast cancer cell line MDA-MB-231 in vitro, which associated with an increase in E-cadherin, beta-catenin, and especially alpha-catenin gene transcription [71]. The results implicate that EpCAM expression can affect cell migration, invasion, and proliferation by enhancing E-cadherin-mediated cell-to-cell adhesion [71]. Recently, EpCAM has been identified as an additional marker for cancer-initiating stem cells [77-80].

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 [72]. EpCAM expressing pancreatic cancer stem cells showed a 100-fold enhanced...

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Figure 1. Revised structural model of EpCAM. (A) Sequence homology between the second EGF-like domain of EpCAM and a repeat from human thyroglobulin (TY). EpCAM is shown with N- (N) and C-terminus (C), signal peptide (SP), transmembrane domain (TM), N-linked carbohydrates (CHO), EGF-like domain (EGF) and TY repeat domain (TY). Sequence identity (red amino acid residues) between EpCAM and a selected TY repeat is 54%. Conserved exchanges are shown in blue. The cognate motif of all TY domains, QCNCxWCV, is highlighted by pink boxes. (B) Old (left) and revised domain model of EpCAM (right). EpCAM is depicted as a tetramer showing three additional subunits with dotted lines. Structural analysis of many TY domains from different proteins has shown that N- and C-termini are in close proximity. This is why the polypeptide chain is depicted with a bent within the TY domain that would orient the EGF-like domain towards the cell membrane. Cleavage sites for two proteases releasing the intracellular portion of EpCAM are indicated by red arrows, and the domain of EpCAM interacting with the listed proteins is shown by a bracket [69].

1. **Growth factors receptors:** Oncogenic receptor EGFRvIII (GBM,NSCLC or MLC, SCC, A431 cells) [11-16], Oncogenic receptor MUC1 [17] or MUC4 [17], Neu oncogenic receptor (breast cancer) [18-20]; Oncogenic receptor EGFR-1R [21]; Oncogenic B receptor (HCD,CLL) [22], pleiotrophin, midkine, BMP9, cytokine augmentor alpha (AUG-alpha) ligands/oncogenic receptor ALK, oncogenic ALK fusion [23-27] and other VEGFR2 (colorectal cancer, glioma) [28,29].

2. **Cytokine receptors:** Oncogenic growth hormone receptor (gigantism,acromegaly) [30,31]; GHRH/GHRHR oncogenic signalling (pituitary tumors); Oncogenic EPOR(PFCP) [32], oncogenic EPO-R/GHR/KG fusion (BCP-ALL) [33]; Oncogenic CSF3-R (CNL or AML) [34]; IL-2-BCM fusion (T cell lymphoma); IL-3-lgH oncogenic fusion(ALL); IL-11/IL-11 receptor (gp130 Y757F/Y757F) pro-oncogenic signalling (gastric tumor in mice) [35,36]; IL-21-BCR fusion (DLBCL, lymphoma cell line); Oncogenic TSHR (thyroid adenoma); proto-oncogenic IL-13 receptor alpha 2.

3. **Steroid receptors:** Oncogenic thyroid hormone receptor(TR) (PTC) [37-39], oncogenic THRI/BRA fusion (breast cancer cell line); oncogenic receptor pml/RARa (APL) [40,41]; Oncogenic receptor AR variants(Pca) [42-48]; ER pro-neoplastic signaling [49-52], neoplastic ESR1-CCDC170 fusion (also oncogenic receptor ESR1 fusion in breast cancer) [8,10,53]; GR aberrant signaling (Cushing's disease, erythrocytosis, GR+ breast cancer, Nelson's syndrome) [54-58]; FSH/FSH receptor oncogenic signalling (preneoplastic ovarian surface epithelial cells).

4. **Others:** Pro-oncogenic receptor CLC1[59]; oncogenic form of EphA2 receptor (SB97, ephrin A1 ligand is anti-oncogenic [60]; Toll-like receptor(TLR4) pro-oncogenic signaling.

5. **Tobacco related cancer** (toxicology: nicotinic acetylcholine receptor alpha7-nAChR oncogenic receptor [61,62].

6. **Environmental pollutants** (toxicology): Oncogenic potential of AhR (aryl hydrocarbon receptor, AhR physiological ligands indole derivatives) [63,64].

tumorigenic potential compared with EpCAM-negative pancreatic cancer stem cells [81-82]. Similarly, in vivo evaluation of tumorigenicity in hepatocellular carcinoma cell lines, using immunodeficient NOG mice, a smaller number of EpCAM+ cells (minimum 100) than EpCAM- cells are able to form tumors. The introduction of exogenous EpCAM into EpCAM+ clones, but not into EpCAM-clones, markedly enhanced their tumor-forming ability [79]. Also, EpCAM-positive hepatocellular carcinoma stem cells could efficiently initiate tumors in SCID mice [80]. Very recent, EpCAM-proliferating ductal cells (PDC) give rise to hepatocellular carcinoma (HCC) in the inflamed liver [82], 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 tumors in SCID mice was for EpCAM+ cells 50-fold greater compared with the unfractioned tumour cells [81]. 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 overexpression is associated with decreased overall survival of patients with a broad variety of carcinoma [75,81].

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 [81,83].
Figure 2. A Scheme of oncogenic receptor (or receptor) mediated multiple signal transduction. Here, nuclear regulators include transcriptional factors such as c-Jun/AP-1, Fos, NF-kB, myc, p53, and RB and so on.
Signal transduction by EpCAM oncogenic receptor and its target pathway

Several biological function of EpCAM have 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 1) From earlier period of Figure 2, three different signaling cascades are clearly shown (see below). Recent advances further uncovers a highlight of new data in its distinct signal pathway.

**PI-3K/Akt and Ras/MAPK signaling pathway, an old thematic topics**

PI turnover: Phospholipase Cr (PLCr) is activated by receptor tyrosine kinase (RTK) through the binding of its SH2 (syc-homology 2) domains to phosphotyrosine sites of the receptor. After activation, PLCr hydrolyses its substrate ptdins (4,5) p2 (PIP2) and forms two second messengers, diacyclglycerol (DAG) and Ins (1,4,5) p3 (IP3). IP3 bind its receptor that stimulates the release of Ca2+ from intracellular stores. DAG activate members of the protein kinase C (PKC) family. Ca2+ then binds to calmodulin, which subsequently activates a family of calmodulin dependent protein kinases (Camks). The second messengers generated by PIP2 hydrolysis stimulate a variety of intracellular processes such as proliferation, angiogenesis, and cell motility [84,85].

PI3-K/Akt pathway: The class phosphatidylinositol 3 kinase (PI3-K) is activated by the majority of oncogenic RTKs. Like other SH2 domain-containing proteins, PI3 kinase forms a complex with a PTB site on activated receptor. The main function of PI3K activation is the generation of PI3P (ptdins (3) p) which function as a second messenger to activate downstream tyrosine kinase Btk and Itk, the ser/thr kinase PDK1 (phoinositide dependent protein kinase 1) and Akt (Protein Kinase B,PKB). The major biological functions of Akt activation is involved in cell survival, anti-apoptosis and proliferation and cell growth. Akt is also known to be implicated in several cancers, particularly breast cancer. Proteins encoded by the Syc oncogenes may function as inositol lipid kinases in convert phosphatidylinositol (PI) into PtdIns (4,5) p2 process [84].

Ras/Raf/MAPK: In ras/MAPK signal pathway, Each of three closely related mammalian ras oncogene (H-ras, K-ras and N-ras) encode a 21-KD protein (p21) of 188 or 189 amino acids which are located at the inner surface of the cell membrane. ras protein are guanine nucleotide binding proteins with a low intrinsic GTPase activity that can switch from an inactive GDP-bound form to an active GTP-bound. The 120kd cytoplasmic protein (referred as GAP, GTPase activating protein) interacts with normal ras GTP at p21 effector site and stimulates its intrinsic GTPase activity dramatically to down-regulate ras GTP. Ras p21 residues thus appear to be required for GAP effector binding. Also, GAP interaction may be essential for ras p21 biological activity. P21 mutated at codons 12, 13 and 61 abolish the intrinsic GTPase activity, the resulting oncogenic protein can still bound GTP. Thus, In the signal transducing G proteins, they are biologically active when in the guanosine triphosphate (GTP)-bound form and inactive when bound to guanosine diphosphate (GDP) [86-89].

GAP is phosphorylated on tyrosine in response to PDF or EGF. After stimulation of cells (in 3T3 cells and in CHO cells) with PDGF, GAP physically associated with PDGF receptor and with PI-3 kinase (3’ phosphatidylinositol kinase,85kd), c-raf (a cytoplasmic serine/threonine kinase, 74kd) and PLC- r (140kd). This association occurs via an SH2 domain of the receptor. A 83 amino acids deletion in the mutant PDGF receptor ("kinase insert domain") that blocks PDGF-induced mitogenesis also blocks binding of PI-3 kinase, but not PLC-r or c-raf. This deletion also blocks GAP binding, implying that GAP and PI-3 kinase are essential components of the mitogenic response.

EGF also increases the binding of GTP to ras p21, whereas GTP-binding protein may thus extended in controlling cyclic AMP production. Thus the association of p21 ras. GAP with ligand-activated PDGF receptor may directly link growth factors and ras signaling transduction from the plasma membrane into the cell [86-90].

Also, the adaptor protein growth factor receptor-bound protein 2 (Grb2) forms a complex with SOS (son of sevenless) protein by the Grb2 SH3 domain. Grb2 or Grb2/SOS complex is recruited to the membrane by the Grb2 SH2 domain binding to activated PDGFR-bound SHP2, thereby allowing interaction with Ras and the exchange of GDP for GTP on Ras via GTPase hydrolysis. Whereas the interaction between Grb2 and activated PDGFR occurs through interaction with the SHP2 protein, Grb2 binds to oncogenic EGFR through Shc, another adaptor protein that forms a complex with many receptors via its phosphotyrosine binding domains (PTB) [86-92]. This Shc-Grb2/EGFR complex activate ras.

After activation, subsequently, Ras interacts with several proteins, namely Raf. Activated Raf stimulates mitogen-activated protein kinase (MAPK) kinase (MAPKK or MEK) by phosphorylating a ser residue in its activation loop. MAPKK then phosphorylates MAPK (ERK1/2) on T or Y residues at the active loop leading to its activation [93-95]. Activated MAPK phosphorylates a variety of cytoplasmic substrates, as well as transcription factors and other kinases, when translocated into nucleus, and thus contribute to the regulation of different cellular processes such as cell survival, proliferation, differentiation, apoptosis and immune responses. At present, Ras/MAPK/ERK/IP3-K/Akt pathway act as the major oncogenic signaling pathway.

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

Adhesion molecules are known to play an important role in defining cell fate, differentiation and other biological characteristics [96]. EpCAM is a Ca2+-independent homotypic intercellular adhesion molecule [66-67], thereby preventing cell scattering and likely to play a role in inhibition of invasion [97,98]. 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 Ca2+-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 [96].

Furthermore, the adhesion function of E-cadherin depends on their association with regulatory proteins, such as alpha- and beta-catenin [96,99-100]. Catenins link cadherins with the actin cytoskeleton and can also form complexes with other epidermal growth factor receptor (EGFR) protein [101]. 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 [73]. This negative effect of EpCAM expression on cadherin-mediated adhesion may explain the association of EpCAM expression with invasion and metastasis in epithelial carcinoma [71,102]. 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 [71], 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 [71,103-104]. Wnt binds to receptors of the Frizzled family on the cell surface. Through several cytoplasmic relay components, the signal is transduced to beta-catenin, which accumulate 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[103].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 [71].This notion is also supported by Yamashita [80] in patients with hepatocellular carcinoma and Kimura [79] 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 EpcD and EpCAM molecules in the nuclei of any cell clones from the PLC/PRF/5 cell lines [79]. Moreover, the hepatic stem cell marker EpCAM knockdown in EpCAM+ cells reduces their colony-forming ability, suggesting an important role for EpCAM in EpCAM+ cells, and, regardless of the exogenous expression of EpCAM, EpCAM+ clones still had higher expression of c-myc, than the EpCAM-overexpressing EpCAM- clones. Therefore, signals through EpCAM induce Wnt/beta-catenin activation might be involved to another different signaling pathway in tumorigenesis under certain condition [79-80,105]

**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 [106,107]. EpCAM was identified as a signal transducer [72]: 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. EpcD 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 [72], and drives cell proliferation. This notion is supported by the EpCAM found in nuclei of colon carcinoma but not of normal tissue [72], and HCT (colon) and MCF-7 (breast) carcinoma cells [65].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 (CRC) and has been shown to facilitate metastasis [108].

Others, epithelial-specific Ets-1 and Sp1 play an active role in EpCAM promoter regulation [69], while transcription factor nuclear factor-kappa B (NF-KB) and p53 have been described as transcriptional repressor of EpCAM [81]. TACE-dependent EGF axis [109,110], Claudin-7 and claudin-1 trafficked into lysosomes [111] and presenilins mediate PI3K/akt and ERK activation via select signaling receptors [112], 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 immunotarget, antibody-based clinical trials and in 2009, the European Medicines Agency approved the use of trifunctional bispecific antibody Catumaxomab, which binds to EpCAM oncogenic receptor and enhances the immunological response against EpCAM-positive cells in malignant ascites [76,113]. Effects of monoclonal antibody immunotherapy was initially trials on patients with gastrointestinal adenocarcinoma [114], 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-colorctal cancer mouse monoclonal antibody 1083-17-1A of the IgG2a immunotherapy. 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 [115]. Indeed, the use of the EpCAM-specific monoclonal antibody has been successful in increasing disease-free survival in colon and breast cancer patients with minimal residual disease [71].

In 1989-91, Zhu 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; 65, 116]. In 1993-June 2002, Zhu at first light included those monoclonal antibodies (MoAb) targeting inhibitors such as bevacizumab [117-119], sorafenib [120,121], trastuzumab, cetuximab, and erlotinib+gefitinib and afatinib, and imatinib in preparation of test book "Pharmacology (Revised chinese edition). Zhu [122,123] also is try to use gefitinib in clinical trials of metastatic lung cancer to improve patient survival. Bevacizumab (Avastin) is approved by Food and Drug Administration (FDA) in May 2009 for the treatment of recurrent glioblastoma multiforme (GBM), resulting in tumor stability [117-119].

Now, several anti-EpCAM therapeutic antibodies have been developed (edrecolomab, ING-1, 3622W94, adecatumumab) [124]. 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[76] and in patients with rising prostate specific antigen (PSA) levels after radical prostatectomy[76]. It is at present reaching phase III trial [125-128].

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[76]. Targeting EpCAM oncogenic receptor might be a promising approach to stop tumor initiation, invasion and progression.

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