Journal of Clinical Neuroscience 44 (2017) 84–88

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

Epithelial membrane protein 2: Molecular interactions and clinical implications

Lawrance K. Chung [a], Nikhilesh S. Bhatt [a], Carlito Lagman [a], Panayiotis E. Pelargos [a], Yu Qin [b], Lynn K. Gordon [c], Madhuri Wadehra [b,d], Isaac Yang [a,d,e,f,*]

[a] Department of Neurosurgery, University of California, Los Angeles, 300 Stein Plaza, Suite 420, Los Angeles, CA 90095, USA
[b] Department of Pathology and Laboratory Medicine, University of California, Los Angeles, 924 Westwood Blvd, Seventh Floor, Los Angeles, CA 90095, USA
[c] Department of Ophthalmology, University of California, Los Angeles, 100 Stein Plaza, Los Angeles, CA 90095, USA
[d] Jonsson Comprehensive Cancer Center, University of California, Los Angeles, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095, USA
[e] Department of Radiation Oncology, University of California, Los Angeles, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095, USA
[f] Department of Head and Neck Surgery, University of California, Los Angeles, 200 UCLA Medical Plaza, Suite 550, Los Angeles, CA 90095, USA

ARTICLE INFO

Article history:
Received 7 April 2017
Accepted 19 June 2017

Keywords:
EMP2
Glioblastoma
Antibody therapy
Epithelial membrane protein 2

ABSTRACT

Epithelial membrane protein 2 (EMP2) is a cell surface protein that has recently emerged as an object of neuro-oncological interest due to its potential to be utilized as a biomarker and target for antibody therapies. Preclinical studies have demonstrated that EMP2 is associated with disease prognosis in a number of human cancers, including glioblastoma. The four large extracellular domains of EMP2 and its association with the extracellular matrix makes it an attractive target for future cancer therapies. Translational research suggests that EMP2 may be targeted with antibodies to improve tumor control and survival in a variety of murine models and cancer types. However, in order to translate these preclinical findings into the clinic, future research will need to focus on elucidating the role EMP2 in the normal human body by better understanding its molecular and chemical interactions. The focus of this review is to provide a comprehensive insight into current research endeavors, discuss the potential for clinically translatable applications, and predict the future directions of such research.

1. Introduction

Epithelial membrane protein 2 (EMP2) is a cell surface protein that has recently emerged as an object of neuro-oncological interest due to its potential to be utilized as a biomarker and target for antibody therapies [1–6]. Notably, EMP2 expression has been found to be upregulated in a number of human cancers and its expression is generally associated with a poor prognosis [7–9]. EMP2 is a member of the growth arrest-specific gene 3/peripheral myelin protein 22 (GAS3/PMP22) tetraspan proteins and is associated with structural and functional alterations in the extracellular membrane (ECM) [2–4]. Given EMP2's four large extracellular domains and association with the ECM in tumors, there are significant efforts dedicated to developing anti-EMP2 antibodies that may one day improve clinical outcomes for cancer patients [1,10].

One area of EMP2 research is in the diagnosis and management of malignant brain tumors. Glioblastoma (GBM) is a primary brain tumor with a strikingly poor prognosis [11–18]. The estimated incidence of GBM is approximately 13,000 individuals per year, with current management consisting of combined surgical resection, radiotherapy, and chemotherapy [13]. However, even with modern treatments and techniques, the median survival for patients is reported to be 15 months [12,19–21]. Accordingly, there is an urgent need for innovative therapeutics for patients with GBM. Thus, the aim of this review on EMP2 is to provide a comprehensive insight into current research endeavors, discuss the potential for clinically translatable applications, and predict the future directions of such research.

2. Normal tissue

EMP2 expression is not uniform throughout the body and varies depending on the organ of interest [22]. Notably, an increase in EMP2 expression does not translate to an increased malignancy across all tissue types, such that in certain cases, a high level of EMP2 expression may be found in both normal tissue and

* Corresponding author at: Department of Neurosurgery, University of California, Los Angeles, 300 Stein Plaza, Suite 562, Los Angeles, CA 90095-1761, USA.
E-mail address: iyang@mednet.ucla.edu (I. Yang).

http://dx.doi.org/10.1016/j.jocn.2017.06.044
0967-5868/

malignant tumors [23]. Thus, understanding the normal expression and distribution of EMP2 in healthy tissues is critical for designing therapeutics that target EMP2. Low amounts of EMP2 mRNA are expressed in the brain, liver, skeletal muscle, prostate, and epididymis [7,23]. Conversely, within tissues of the heart, thyroid, uterus and eyes there are moderate levels of EMP2 expression [23–25]. However, while EMP2 mRNA is observed in these tissues, its protein expression is more selective. In the eye, EMP2 is not expressed on the lens or retina but is found on the cornea, ciliary body, retinal-pigmented epithelial choroid, sclera, iris and optic nerve [25]. The lung has been reported to naturally express a high amount of EMP2 [26]. Consequently, it appears that there is a heterogeneous distribution of EMP2 expression throughout the body [22,23].

3. Molecular interactions

3.1. EMP2 downstream effects

Integrin expression modulates cell invasion and migration properties, which can enhance tumor aggression and growth [27,28]. Studies have found that integrins are partially controlled by members of the tetraspanin family [29]. Given that EMP2's amino acid sequence is 33–43% similar to that of the tetraspanins, it is possible that EMP2 may also influence integrin expression [30]. Wadehra et al. found that EMP2 and β1 integrins are simultaneously expressed in 60% of NIHT3 fibroblast cells; thus, one well-supported hypothesis proposes that EMP2 regulates cell migration and invasion through β1 integrins [4]. The influence of EMP2 on integrins has been validated in several studies including those by Morales et al. which showed a similar influence of EMP2 within ARPE-19 cells, a retinal pigmented epithelial cell line, and in recent studies by Lesko et al. in MDCK cells, a canine kidney epithelial cell line [31,32]. The presence of β1 integrin residing on the cell surface has been observed to lead to changes in the surrounding ECM that further promotes tumor progression [4].

EMP2 regulates caveolin-1 expression and alters cellular processes that may be associated with tumor growth. Caveolae are functionally important for endocytosis, intracellular signaling, and prevention of oncogenic transformations [33–36]. Caveolin-1, the main integral component of the caveolae plasma membranes that facilitates caveolae-mediated cellular signaling, displays tumor-suppressing functions, and is essential for stability of the plasma membrane [33,37–39]. A recent experiment found that when EMP2 expression was upregulated, significantly less caveolin-1 was expressed and, as a result, portions of the cell membrane were internalized [33]. Reduced expression of caveolin-1 and internalization of the cell membrane is associated with cellular transformations linked to the development of various cancers [4,33,40]. Accordingly, EMP2 expression may be critical for cellular homeostasis and the development of oncogenic properties via modulation of caveolin-1.

EMP2 has also been found to associate with focal adhesion kinase (FAK) and Src signaling proteins, suggesting that EMP2 may foster increased cellular motility and proliferation [24]. Fu et al. conducted a study that examined the relationship between EMP2 and FAK/Src in endometrial cancer cells and found that an increase in EMP2 expression was correlated with high FAK/Src activation via phosphorylation [24]. Subsequently, it was proposed that EMP2 and FAK/Src likely create a single complex and that the combined proteins perform signaling functions to maneuver within lipid raft domains. Because enhanced maneuverability has been observed to lead to increased cell migration, it has been suggested that increases in the EMP2-FAK/Src complex may be a driving factor in tumorigenesis and tumor invasion [24].

3.2. Upstream control of EMP2

In healthy endometrial cells, steroid hormones such as progesterone and estrogen have been found to regulate EMP2 levels through cell membrane modifications. In murine models, upregulation of these hormones demonstrated an increase in EMP2 mRNA transcription [41]. However, further studies revealed that an increase in EMP2 translation was caused only by progesterone [41]. Moreover, increased cell membrane translocation of EMP2 was noted as progesterone levels increased. However, this response was delayed, leading the authors to conclude that progesterone likely acts as part of a cascade of reactions that assist in transporting EMP2 to the cell membrane surface [41].

4. Clinical importance

4.1. Biomarker – diagnostic and prognostic factors

With the aid of positron emission tomography (PET), EMP2 expression can be imaged and potentially utilized for diagnostic purposes. Fu et al. established the feasibility of using micro-PET imaging to identify EMP2 positive endometrial tumor cells in a murine model [22]. By conjugating an anti-EMP2 antibody fragment to radiolabeled copper, EMP2 positive tumors were distinctly and accurately identified while EMP2 negative tissues remained dull. This approach has the potential to provide prognostic value as micro-PET allows the intensity of EMP2 positive tumors to be quantitatively measured. Specifically, the intensity of EMP2 expression on micro-PET has been found to be associated with the lesion's histological grade. Accordingly, the intensity of EMP2 expression on micro-PET can be used as a rough prediction of tumor grade and decrease the need to perform invasive biopsies to obtain a prognosis. Considering that EMP2 expression has also been found in many cancer types, this non-invasive prognostic method may potentially be applied to treatment algorithms for endometrial cancers, ovarian cancers, breast cancers, GBM, urinary bladder urothelial carcinoma (UBUC), and nasopharyngeal carcinoma (NPC) [1,3,7,42,43].

It is important to note, however, that the correlation between EMP2 expression and histological grade is variable. In endometrial cancers, ovarian cancers, and GBM, higher grades correspond with higher EMP2 levels [3,4,42]. However, for UBUC and NPC, EMP2 expression is inversely related to tumor grade. In both of these cancers, low EMP2 levels correspond to a higher grade and, therefore, a poorer prognosis. In UBUC, EMP2 decreases cell viability and proliferation by increasing tumor necrosis [1]. Similarly, in NPC, EMP2 acts as a tumor suppressor; thus, low EMP2 levels facilitate tumor growth [43].

Genetic mutations of EMP2 have also been explored for diagnosis and mapping purposes. In a small sample of patients with nephrotic syndrome, mutations in the EMP2 gene were identified in the glomeruli of the kidney [44]. Subsequently, the link between EMP2 and nephrotic syndrome was explored through *in vivo* and *in vitro* knockdown studies of *EMP2*. This manipulation caused increased pericardial effusions in zebrafish, and decreased cell proliferation in human podocytes and endothelial cells, supporting the pathogenic role of mutated *EMP2* in human nephrotic syndrome. Ultimately, the researchers concluded that *EMP2* mutations led to a recessive Mendelian form of nephrotic syndrome. Moreover, Street et al. attempted to determine if an EMP2 mutation was responsible for causing autosomal dominant Charcot-Marie-Tooth type 1C (CMT1C) disease [45]. According to haplotype analysis and genetic sequencing in two families, the CMT1C gene was mapped to chromosome 16p13.1-p12.3 while the EMP2 gene was mapped to chromosome 16p13.2. Although the CMT1C gene