Critical Role of a Novel Biological Marker GALNT14 Expression in Different Cancer Types

Yonca Erdal[1], Kubilay Dogan Kılıc[2], Hatice K Basaloglu[3] and Mehmet Turgut[3,4*]

[1]Department of Stem Cell, Ege University, Institute of Health Sciences, Izmir, Turkey

[2]Department of Histology and Embryology, Ege University, School of Medicine, Izmir, Turkey

[3]Department of Histology and Embryology, Adnan Menderes University, School of Medicine, Aydın, Turkey

[4]Department of Neurosurgery, Adnan Menderes University School of Medicine, Aydın, Turkey

*Corresponding author: Mehmet Turgut , Associate Professor of Neurosurgery, Department of Neurosurgery, Adnan Menderes University School of Medicine, 09100 Aydın, Turkey, Fax: +90 256 2120146; Tel: +90 256 2134874; E-mail: drmturgut@yahoo.com

GALNT and GALNT14

O type-glycosylation which binding of monosaccharides to Ser and Thr residues on receptor proteins is one of the most common post-translational modifications. It regulates a variety of biological processes that including cell growth, signaling, protein stability and traffic analysis and cell adhesion [1]. O-type glycosylation is present in humans with at least 20 members, from GALNTl to 14 and from GALNTI to L6. It is catalyzed by GalNAc transferases which a large polypeptide in the Golgi complex [2]. In addition to their role in normal cellular processes, changes in O-glycan compositions alter GALNT expression and cause cancer.

GALNT14 changes cell migration and cellular morphology. Over expression of GALNT14 causes malignancies in many organs in human body. We can see breast, ovarium, lungs and skin in previous researches [2-5]. It has also been associated with neuroblastoma and colorectal cancer in gene expression experiments performed [6,7]. GALNT14 expression is a potential biomarker for different cancers including breast cancer and it is likely to play a role in the regulation of apoptotic activity of insulin-like growth factor binding protein-3. GALNT14, a catalytic enzyme, catalyzes a number of proteins such as the gene product death receptors DR-4 and 5 [7]. GALNT14 mediated death-receptor O-glycosylation regulates tumor-cell sensitivity to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [3].

GALNT4 and Breast Cancer

Although breast cancer mortality is reduced by current treatments, more than 450,000 deaths are expected each year due to breast cancer [8]. Tumor metastasis of breast cancer stil significantly reduces survival [9]. One of the proteins that cause metastasis is the GALNT family. GALNT14 causes the onset of the metastatic colony and has been reported to increase the progression of metastases and direct breast cancer metastasis to the lung [1].

Overexpression of GALNT14 plays a critical role in cell migration, invasion and proliferation of breast cancer by stimulating the epithelial mesenchymal transition of breast cancer cells [6]. In addition, GALNT14 promotes self-renewal of cells in breast cancer and supports breast cancer cells to metastasize into the lung micro-environment by inhibiting the effect of lung-derived bone morphogenetic proteins. Additively, GALNT14 is not only causes macrophage infiltration, it also supports the continuous growth of breast cancer cells in the lung by neutralizing macrophage-derived fibroblast growth factors [1]. GALNT14 increases migration by altering the proliferation rate of breast cancer cells and thus induce metastasis. Therefore, it has been suggested that this gene is a new therapeutic target for breast cancer [6].

GALNT14 and Over Cancer

Ovarian cancer is the fifth cause of cancer mortality among women population around the world, with about 225,500 new cases occurring annually [10]. Among gynecologic malignancies, epithelial over carcinoma is the most aggressive one. It can be cured in early stage by surgery and chemotherapy, effectively. GALNT14 is frequently elevated in over cancer cells and regulates cellular migration and cellular morphological properties in over cancer cells.

GALNT14 contributes to over-carcinogenesis via abnormal glycosylation of Mucin 13 [3]. MUC 13 is a high molecular weight transmembrane O-type linked glycoprotein secreted by the epithelium and it is expressed highly in epithelial tumor cells. At the same time, MUC 13 is a prognostic molecular biomarker in some tumors [11]. It has been found that the ERK1/2 inhibit or modulates the expression level of GALNT14. Accordingly, GALNT14 suggests that ERK1/2 is a downstream signaling molecule in regulating cellular biological behavior. New information about the pathophysiological role of GALNT14, which plays a role in over cancer progression using the ERK signaling pathway, can be obtained [3].

GALNT 14 and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common solid cancer in the world and the third leading cancer of cancer-related deaths [12]. Early stage HCC can be treated surgically, by ablation procedures or by liver transplantation [13]. Hepatitis B and C viruses are the main causes of HCC [14]. Recently, some genomic variants of GALNT14 were found as an important predictors for responses to chemotherapy in HCC patients. According to recent studies, a single nucleotide polymorphism on GALNT14 is shown to be associated with the therapeutic response to combined chemotherapy in cases with advanced HCC. The gene region that encoded GALNT14 associated to time-to-progression and survival in patinets with HCC [12,13].

GALNT 14 and Non-small Cell Lung Cancer

Non-small Cell Lung Cancer (NSCLC) is one of the most common lung cancers with a lethal and aggressive malignancy. It is known that it has low sensitivity to chemotherapy and even with the best

treatment, it has high mortality [15]. Histologically, NSCLC is the most common type of lung cancer that constitutes 85% of all cases with lung cancer. Etiologically, smoking is the main cause of NSCLC but age, sex, ethnicity, body weight, infections, environment and other lung diseases, airway obstruction also affects NSCLC [16]. Recent studies have found a relationship between GALNT14 and NSCLC, it is a biomarker for NSCL. High expression of GALNT14 in tumor cells is associated with Apo2L / TRAIL sensitivity. In addition, GaLNT14 expression may be a sign of poor prognosis in cases with advanced stage of NSCLC. However, treatment studies related to GALNT14-NSCLC are inadequate and studies should continue in future [4].

References

1. Song KH, Park MS, Nandu, TS, Gadad S, Kim SC, et al. (2016) GALNT14 promotes lung-specific breast cancer metastasis by modulating self-renewal and interaction with the lung microenvironment. Nat Commun 7.

2. Huanna T, Tao Z, Xiangfei W, Longfei A, Yuanyuan X, et al. (2015) GALNT14 mediates tumor invasion and migration in breast cancer cell MCF-7. Mol Carcinog 54: 1159-1171.

3. Wang R, Yu C, Zhao D, Wu M, Yang Z (2013) The mucin-type glycosylating enzyme polypeptide N-acetyl galactosaminyl transferase 14 promotes the migration of ovarian cancer by modifying mucin 13. OncolRep 30: 667-676.

4. SyriaJC, Mark Z, Zatloukal P, Szima B, Albert I, et al. (2011) Randomized phase II study of dulanermin in combination with paclitaxel, carboplatin, and bevacizumab in advanced non–small-cell lung cancer. J ClinOncol 29: 4442-4451.

5. Wagner KW, Punnoose EA, Januario T, Lawrence DA, Pitti RM, et al. (2007) Death-receptor O-glycosylation controls tumor-cell sensitivity to the proapoptotic ligand Apo2L/TRAIL. NatMed 13: 1070-1077.

6. De Mariano M, Gallesio R, Chierici M, Furlanello C, Conte M, et al. (2015) Identification of GALNT14 as a novel neuroblastoma predisposition gene. Oncotarget 6: 26335.

7. Lin WR, Chiang JM, Liang KH, Lim SN, Lai MW, et al. (2016) GALNT14 Genotype predicts postoperative outcome of stage III colorectal cancer with oxaliplatin as adjuvant chemotherapy. Medicine 95.

8. Prat A, Pineda E, Adamo B, Galván P, Fernández A, et al. (2015) Clinical implications of the intrinsic molecular subtypes of breast cancer. TheBreast 24: 526-535.

9. Zhang C, Xu Y, Hao Q, Wang S, Li H, et al. (2015) FOXP3 suppresses breast cancer metastasis through down regulation of CD44. Int J Cancer 137: 1279-1290.

10. French JD, Johnatty SE, Lu Y, Beesley J, Gao B, et al. (2016) Germline polymorphisms in an enhancer of PSIP1 are associated with progression-freesurvival in epithelial ovarian cancer. Oncotarget 7: 6353.

11. Wang H, Shen L, Lin Y, Shi Q, Yang Y, et al. (2015) The expression and prognostic significance of Mucin 13 and Mucin 20 in esophageal squamous cell carcinoma. J Cancer Res Ther 11: 74.

12. Yeh CT, Liang KH, Lin CC, Chang ML, Hsu CL, et al. (2014) A single nucleotide polymorphism on the GALNT14 gene as an effective predictor of response to chemotherapy in advanced hepatocellular carcinoma. Int J Cancer 134: 1214-1224.

13. Liang KH, Lin CL, Chen SF, Chiu CW, Yang PC, et al. (2016) GALNT14 genotype effectively predicts the therapeutic response in unresectable hepatocellular carcinoma treated with transcatheter arterial chemoembolization. Pharmacogenomics17: 353-366.

14. Liang KH, Yang PC, Yeh CT (2014) Genotyping the GALNT14 gene by joint analysis of two linked single nucleotide polymorphisms using liver tissues for clinical and geographical comparisons. Oncol Lett 8: 2215-2220.

15. Qu X, LiuJ, Zhong X, LiX, ZhangQ (2016) Role of AXL expression in non-small cell lung cancer. Oncol Lett 12: 5085-5091.

16. Jia M, ZhuM, ZhouF, WangM, Sun M, et al. (2017) Genetic variants of JNK and p38α pathways and risk of non-small cell lung cancer in an Eastern Chinese population. Int J Cancer 140: 807-817.