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The role of zinc finger E-box-binding homeoboxin the prognosis of Glioblastoma: A review

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Abstract

Glioblastoma is one of the most malignant brain tumors that have a low survival rate compared to other cancers. The hallmark of tumor metastasis is controlled by a process called epithelial-mesenchymal transition (EMT). The EMT can also be affected by a protein called Zinc finger E-box-binding homeobox 1 encoded by the ZEB1 gene. Studies have found that this gene is expressed by the primary glioblastomas. This gene is localized in the invasion front of the tumor which also has fewer N-cadherin expression, another protein associated with the EMT process. The lower the N-cadherin expression, the less cell-cell connections and the greater the cell mobility, which means increased invasiveness. Therefore, redistributing the N-cadherin expression, such as by using the ROBO1, is a promising way to control the glioblastoma invasion. Coincidentally, the ROBO1 expression can be controlled by the expression of the ZEB1 gene. There is also a paralog of the ZEB1 gene, namely the ZEB2 gene which plays a role in Transforming growth factor beta (TGF-β) signaling pathways, which is positively correlated with aggressiveness of the cancers. In fact, studies have found that higher expression of the ZEB2 gene is correlated with lower survival rate of glioblastoma patients.

Keywords: Glioblastoma; EMT; ZEB1; N-cadherin

1. Introduction

Glioblastoma is one of the most aggressive types of primary brain neoplasm that have limited treatment options [1]. The survival rates have not changed dramatically during many years, especially when compared to other cancers. Glioblastoma is derived from the astrocyte cell type. Grade 1 astrocytomas are considered benign and slow growing. Grade 2 astrocytomas are more aggressive, more likely to recur or progress over time. Grade 3 and 4 astrocytomas are considered high grade glioblastomas [2]. Epithelial-mesenchymal transition is a process which allows a polarized epithelial cell to undergo multiple biochemical changes that enable it to transition its phenotype properties into mesenchymal cell, which includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and production of extracellular matrix (ECM) components. These changes in properties are what is believed to be the factor that allows cancers to migrate from its primary site and invade other organs. There are three types of EMT, the type 1 EMT that occurs during implantation, embryogenesis, and organ development, type 2 EMT which is associated with tissue regeneration and organ fibrosis, and type 3 EMT that is associated with cancer progression and metastasis [3]. Zinc finger E-box-binding homeobox 1 is a protein in humans encoded by the ZEB1 gene. ZEB1 downregulates E-cadherin and induces EMT which plays a role in cancer cell migration and invasion [4,5]. ZEB1 paralog, ZEB2, plays a role in the Transforming growth factor beta (TGF-β) signaling pathways. TGF-β upregulates integrin α3, which is positively correlated to cancer cells aggressiveness [5,6]. Present studies on these two zinc finger proteins which were expressed highly in glioblastoma cells allow us to analyze the promising prognostic factor of these proteins on glioblastoma.

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2. Expression of ZEB1 in Glioblastoma

Researchers found that different levels of tumor invasion in xenograft models were observed utilizing three cell lines derived from primary glioblastoma specimens (human Glioblastoma (hGBM) L0, L1, and L2) [7,8]. Tumor cells moved along the subcortical white matter across the midline in every instance, following the brain's anatomical pattern. EMT-related factors may also control the invasion of brain tumors. Therefore, the expression of EMT-associated factors in cell lines was examined, and it was discovered that N-cadherin and ZEB1, ZEB2, Twist1, and Engrailed1 are expressed in all three lines. Snail, Slug, and E-cadherin, on the other hand, were only discovered in one line. The Cancer Genome Atlas (TCGA) dataset's analysis of these variables found that only ZEB1 significantly correlated with patient survival [9].

In tumor xenografts, ZEB1 is preferentially localized along the invasion front. N-cadherin expression is limited to the tumor bulk and diminishes toward the invasion front; invasive cells do not express N-cadherin [10]. Notably, it has been shown that N-cadherin expression and invasion are inversely related, and that cell-cell contacts are crucial for the processes of EMT and plasticity [11]. ZEB1 expression is known to be induced by beta-catenin. Reduced cell-cell interactions during invasion were corroborated by the immunoreactivity's localization to the cell membranes within the tumor core and its absence at the invasion front. ZEB1 may play a regulatory role in glioblastoma invasion due to the coincidence of its positive population with the distal-most invading tumor cells, leading researchers to try and pinpoint its precise roles in glioblastoma [12,13].

2.1. ZEB1 Pathway Associated with Glioblastoma

Invading glioblastoma cells with decreased membrane-associated N-cadherin have fewer cell connections, which increases the invasiveness of ZEB1-positive cells. Contrary to what immunofluorescent studies of xenografted tumours suggested, invasive tumors did not express N-cadherin. Overall N-cadherin protein levels between ZEB1 knockdown and controls did not differ, according to a Western analysis. The key distinction for tumor cell attachment may be found in the distribution of N-cadherin. The different membrane location of this protein between control and ZEB1 knockdown cells was further demonstrated by N-cadherin immunostaining. N-cadherin protein equally stippled the cell membrane in normal cells, while ZEB1 knockdown concentrated N-cadherin to the membranes that were juxtaposed between adjacent cells. Greater cell mobility may be explained by redistributing N-cadherin away from the point of contact between cells, which can be accomplished if N-cadherin is severed from its intracellular cytoskeleton anchor. The N-anchoring cadherin's to the cytoskeleton can be severed by the axon guidance molecule ROBO1, which is expressed in malignant glioblastomas and increases cellular motility [14,15].

ROBO1 was identified as a potential target of the ZEB1 regulatory loop after a database search for microRNA binding sites [16,17]. ROBO1 serves as an intermediate invasion regulator as a result. ROBO1 expression levels were decreased by ZEB1 knockdown, whereas ZEB1 overexpression had the reverse impact. Additionally, ZEB1 knockdown cells lack ROBO1, although control cells do have it at the outer membrane. ROBO1 expression was either lowered or raised when miR-200c was overexpressed or antagonistic. Similar to how they did with ZEB1 overexpression and knockdown cells, these modifications returned ROBO1 expression to normal levels. Increased invasiveness of xenograft tumors caused by forced expression of ZEB1 was observed, with tumor cells spreading widely along white matter tracts. In tumors, ROBO1 expression rises toward the front of invasion and is inversely correlated with N-cadherin expression. Overexpressing ROBO1 was able to restore the migratory phenotype in ZEB1 knockdown cells, but inhibiting ROBO1 significantly inhibited the migration of ZEB1 overexpressing cells. ZEB1 controls ROBO1, and ROBO1 is a promising candidate molecule for controlling glioblastoma invasion [18].

2.2. The Role of ZEB as a Prognostic Biomarker

Cadherins play an important role in the developmental processes and epithelial tumorigenesis in the form of a process known as EMT. E-cadherin is known to inhibit the process of EMT. The process of EMT is regulated by proteins such as SNAIL, SLUG, E47, and ZEB, which is known to downregulate the expression of E-cadherin. This downregulation of E-cadherin is what is believed to be the hallmark of tumor metastasis [19,20]. A retrospective study found a tumoral expression of SLUG, ZEB1, or ZEB2 in almost 60% of all the metastatic brain lesions analyzed with a significantly higher proportion of expression in the metastases than the primary tumor [21]. The expression ZEB family proteins is already known as one of the centerpieces in the metastasis process of tumors. A study by Chen et al, 2018 was conducted to screen the potential correlation between ZEB 1 and 2 expression and clinicopathological factors to screen the potential parameters relevant to ZEB overexpression. There was no significant association with ZEB1 or 2 expression observed among all the detected clinicopathological factors evaluated in the study. However, high expression of ZEB2 was significantly associated with lower survival of GBM patients. There was no significant association found between ZEB1 and the overall survival rate from this study [20]. High expression of ZEB2 and TGF-β1 was also found in epithelial ovarian cancer patients which may contribute to the prognosis of the tumor [22].

3. Conclusion

These proteins expressed by the tumors may give possibilities as a marker for the prognosis of tumors, especially ZEB2 on the glioblastomas, however more studies need to be conducted to bring a more significant impact regarding this topic.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in the creation of this article.

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