doi 10.18699/CRISPR-2025-80

Can ZEB1 be a prognostic factor for uveal melanoma?

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Key words: uveal melanoma; ZEB1; VEGF-A

Melanoma is a heterogeneous disease that includes tumors of various localizations. Uveal melanoma (UM) is the most prevalent primary ocular cancer, representing 5% of all melanomas. UM and cutaneous melanoma (CM) have the same melanocytic origin, however genetic and molecular changes in cancer are different for the uveal melanocytes and skin melanocytes, as well as spread of metastases. Thus, targeted drugs for the treatment of CM are usually ineffective for UM. This is primarily due to the fact the eye is an immunologically privileged organ, and it fails to achieve efficacy of immune checkpoint inhibitors (ICIs) comparable to that for CM. Moreover, there is a poor understanding of the role of epithelial-to-mesenchymal transition (EMT) in UM progression. These features of UM bring it closer to brain tumors, as well as low sensitivity to immunotherapy, and actualize the search for new approaches to the treatment of the highly lethal metastatic form of UM.

Since hypoxia is a major stimulator of EMT, in this study we looked at the interaction of the hypoxia-related genes: ZEB1, VEGF-A and VEGFR, and metastatic potential of these UM cells in vivo. Eight personal UM cell cultures previously obtained in the laboratory from tumor samples were used as models. The transcriptional and translational response to hypoxia of the ZEB1, TWIST1, VEGF-A, and FLT1 (VEGFR) genes was studied, as well as the effect of knockdown of these genes and targeted VEGF-A inhibitor Eylea (Aflibercept) on cell viability. Eylea is a soluble decoy receptor, with substantially higher affinity than conventional soluble VEGF receptors.

We showed that the ZEB1 response of UM cells to hypoxia is associated with basal ZEB1 levels, and cells with ZEB1-/low phenotype have greater plasticity in response to hypoxia. Most lines with the ZEB1- phenotype increased ZEB1 production in response to hypoxia, but there were lines in which hypoxia did not change the ZEB1- phenotype. At the same time, cells with a high basal level of ZEB1 decreased the protein level in response to hypoxia. Another feature of the cell with ZEB1- phenotype was the lack of the increase of VEGF-A synthesis in response to hypoxia, and which was observed for cells with the ZEB1+ phenotype.

We suppose that better understanding of the relationship between ZEB1 and VEGF-A may bring new approach for preventing metastasis of UM cells and help confirm ZEB1 as a prognostic marker.

Funding: The study is supported by the grant of the Russian Science Foundation No. 23-14-00285 and was realized within Russian state-funded project for ICBFM SB RAS No. 121030200173-6.