Transglutaminase 2

Expansion of chondrocytes for repair of articular cartilage can lead to dedifferentiation, making it difficult to obtain a sufficient quantity of chondrocytes. Although previous studies have suggested that culture in a three-dimensional environment induces redifferentiation of dedifferentiated chondrocytes, its underlying mechanisms are still poorly understood in terms of metabolism compared with a two-dimensional environment. In this study, we demonstrate that attenuation of transglutaminase 2 (TG2), a multifunctional enzyme, stimulates redifferentiation of dedifferentiated chondrocytes. Fibroblast-like morphological changes increased as TG2 expression increased in passage-dependent manner. When dedifferentiated chondrocytes were cultured in a pellet culture system, TG2 expression was reduced and glycolytic enzyme expression up-regulated. Previous studies demonstrated that TG2 influences energy metabolism, and impaired glycolytic metabolism causes chondrocyte dedifferentiation. Interestingly, TG2 knockdown improved chondrogenic gene expression, glycolytic enzyme expression, and lactate production in a monolayer culture system. Taken together, down-regulation of TG2 is involved in redifferentiaton of dedifferentiated chondrocytes through enhancing glucose metabolism [1)].

Necrosis is a hallmark of glioblastoma (GBM) and is responsible for poor prognosis and resistance to conventional therapies. However, the molecular mechanisms underlying necrotic microenvironment-induced malignancy of GBM have not been elucidated. Here, we report that transglutaminase 2 (TGM2) is upregulated in the perinecrotic region of GBM and triggered mesenchymal (MES) transdifferentiation of glioma stem cells (GSC) by regulating master transcription factors (TF), such as C/EBPβ, TAZ, and STAT3. TGM2 expression was induced by macrophages/microglia-derived cytokines via NF-κB activation and further degraded DNA damage-inducible transcript 3 (GADD153) to induce C/EBPβ expression, resulting in expression of the MES transcriptome. Downregulation of TGM2 decreased sphere-forming ability, tumor size, and radioresistance and survival in a xenograft mouse model through a loss of the MES signature. A TGM2-specific inhibitor GK921 blocked MES transdifferentiation and showed significant therapeutic efficacy in mouse models of GSC. Moreover, TGM2 expression was significantly increased in recurrent MES patients and inversely correlated with patient prognosis. Collectively, our results indicate that TGM2 is a key molecular switch of necrosis-induced MES transdifferentiation and an important therapeutic target for MES GBM. Cancer Res; 77(18); 4973-84. ©2017 AACR [2)].

Bexarotene, a selective retinoid X receptor agonist, showed strong inhibition of neurospheroidal colony formation and migration of cultured primary GBM cells. Bexarotene treatment reduced nestin expression, while significantly increasing glial fibrillary acidic protein (GFAP) expression. The effect of bexarotene on gene expression profile was compared with the activity of all-trans retinoic acid (ATRA), a well-known differentiation inducer. Both drugs largely altered the gene expression pattern into a tumor-ameliorating direction. These drugs increased the gene expression levels of Krüppel-like factor 9 (KLF9), regulator of G-protein signaling 4 (RGS4), growth differentiation factor 15 (GDF15), angiopoietin-like protein 4 (ANGPTL4), and lowered the level of chemokine receptor type 4 (CXCR4). However, transglutaminase 2 (TG2) induction, an adverse effect of ATRA, was much weaker in bexarotene treated primary GBM cells. Consistently, the TG2 enzymatic activity was negligibly affected by bexarotene treatment. It is important to control TG2 overexpression since its upregulation is correlated with tumor transformation and drug resistance. Bexarotene also showed in vivo tumoricidal effects in a GBM xenograft mouse model. Therefore, we suggest bexarotene as a more

beneficial differentiation agent than ATRA for GBM [3].

The TGM2 expression level was associated with increasing WHO malignancy grade as well as meningioma recurrence. Inhibition of TGM2 function by siRNA or cystamine induced meningioma cell death, which was associated with reduced AKT phosphorylation and caspase-3 activation. Collectively, these findings suggest that TGM2 expression increases as a function of malignancy grade and tumor recurrence and that inhibition of TGM2 reduces meningioma cell growth [4].

1)
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