Tissue transglutaminase (tTG), a dual-function enzyme with GTP-binding and acyltransferase activities, has been implicated in the survival and chemotherapy resistance of aggressive cancer cells and cancer stem cells, including glioma stem cells (GSCs). Using a model system comprising two distinct subtypes of GSCs referred to as proneural (PN) and mesenchymal (MES), we find that the phenotypically aggressive and radiation therapy-resistant MES GSCs exclusively express tTG relative to PN GSCs. As such, the self-renewal, proliferation, and survival of these cells was sensitive to treatment with tTG inhibitors, with a benefit being observed when combined with the standard of care for high grade gliomas (i.e. radiation or temozolomide). Efforts to understand the molecular drivers of tTG expression in MES GSCs revealed an unexpected link between tTG and a common marker for stem cells and cancer stem cells, Aldehyde dehydrogenase 1A3 (ALDH1A3). ALDH1A3, as well as other members of the ALDH1 subfamily, can function in cells as a retinaldehyde dehydrogenase to generate retinoic acid (RA) from retinal. We show that the enzymatic activity of ALDH1A3 and its product, RA, are necessary for the observed expression of tTG in MES GSCs. Additionally, the ectopic expression of ALDH1A3 in PN GSCs is sufficient to induce the expression of tTG in these cells, further demonstrating a causal link between ALDH1A3 and tTG. Together, these findings ascribe a novel function for ALDH1A3 in an aggressive GSC phenotype via the up-regulation of tTG, and suggest the potential for a similar role by ALDH1 family members across cancer types [1)].

1)
Sullivan KE, Rojas K, Cerione RA, Nakano I, Wilson KF. The stem cell/cancer stem cell marker ALDH1A3 regulates the expression of the survival factor tissue transglutaminase, in mesenchymal glioma stem cells. Oncotarget. 2017 Apr 4;8(14):22325-22343. doi: 10.18632/oncotarget.16479. PubMed PMID: 28423611; PubMed Central PMCID: PMC5410226.