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Abstract Title: Linking maternal sugar consumption to progenies' developmental defect: a focus on OTX2's O-GlcNAcylation.

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Currently, the average American eats around 22 teaspoons of added sugar every day (~30 sugar cubes/day hidden in foods). This modern glucose-rich diet correlates with an increase of obesity, type 2 or gestational diabetes and is measurable throughout generations. Therefore, determining the interplay between diet and metabolic development is of utmost importance for public health. The O-GlcNAc post-translational modification is a unique glucose rheostat for cell signaling. The addition of a single residue of N-acetylglucosamine on serine and threonine constitutes a simple but highly effective way to sense glucose concentration and regulate protein function. Indeed, the level of extracellular glucose are reflected by the level of UDP-GlcNAc primary substrate for O-GlcNAcylation. To date, thousands of O-GlcNAcylated proteins have been identified. Numerous physiological and pathological processes are O-GlcNAc-regulated such as cell cycle, transcriptional regulation, diabetes, cardiovascular diseases, neurodegeneration and cancers. While O-GlcNAcylation is known to regulate many developmental factors such as homeobox proteins, we are only starting to unravel the impact of O-GlcNAc degulation on developmental defects.
In this study, we have demonstrated that a progeny's O-GlcNAcylation levels are disproportionately affected in response to mother's high sugar diet. Using hyper-O-GlcNAcylated cellular and mouse models, the homeobox protein OTX2 was identified as a major O-GlcNAcylated protein in the developing brain. We have also shown that both transcription and stability of OTX2 were affected by O-GlcNAc variation, resulting in an increased half-life of this protein. Interestingly, we have discovered that while endogenous OTX2 was processed by the proteasome, overexpression in Hela cells resulted in autophagy-mediated degradation. Nevertheless, both degradation processes were inhibited by increased O-GlcNAcylation. Using specific domain contructs, we have discovered that the Retention Domain of OTX2 is highly O-GlcNAcylated, potentially affecting localization and critical phosphorylation sites. Like many homeobox proteins, OTX2 level needs to be tightly regulated for proper patterning and development. Therefore, deregulation of OTX2 amongst other proteins in brain hyper-O-GlcNAcylated mouse results in major developmental defects. Usually supported by a local transient expression of OTX2, pituitary's ontogeny is particularly affected by increase in O-GlcNAc level and is reflected by metabolic defect in adults.

To summarize, this study highlights the O-GlcNAc modification as a nutrient-dependent sensor that regulates the homeobox protein OTX2 during brain development.