**WNT Signaling Promotes Gastric Tumorigenesis by Galectin-3 Mediated Activation of STAT3 Pathway**

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BACKGROUND: Aberrant activation of WNT signaling pathway is known to play a critical role in gastric tumorigenesis. Interestingly, we detected activated STAT3, another key player in gastric tumorigenesis, by WNT1 overexpression. Therefore, we demonstrated how these two pathways are closely regulates gastric tumorigenesis.

HYPOTHESIS: Overexpression of WNT1 increases the expression of galectin-3 and the interaction of galectin-3 with JAK2. This interaction induces STAT3 phosphorylation and nuclear localization, consequently to lead gastric tumorigenesis

METHODS: We performed the clinicopathological analysis in malignant stomach tissues from K19-WNT1 transgenic mice and those from gastric cancer patients. The molecular mechanisms were determined by biochemical assay.

RESULTS: Increased expression of phosphorylated STAT3 and galectin-3 was detected in malignant stomach tissues of K19-WNT1 transgenic mouse, whereas expression of phosphorylated STAT3 was decreased in stomach tissues of K19-WNT1 transgenic-lgals3$^{-/-}$ mice and in lgals3$^{-/-}$ mouse embryo fibroblast cells. We determined that over-expression of WNT1 increased the phosphorylation and nuclear-localization of STAT3 in gastric cancer cells, but ablation of galectin-3 reversed these effects. The STAT3 phosphorylation was caused by interaction between galectin-3 and JAK2. Consequently, galectin-3 was co-translocalized with STAT3 into the nucleus and increased transcriptional activity of STAT3. Galectin-3-depleted gastric cancer cells xenografted mice displayed tumor growth retardation, which was reversed by overexpression of constitutive-activated STAT3. Moreover, high-expression and co-localization of β-catenin, phosphorylated STAT3 and galectin-3 was detected in malignant tissues of gastric cancer patients. Therefore, we performed in this study that WNT1 increases expression of galectin-3 and then phosphorylates STAT3 by the interaction of galectin-3 and JAK2 to lead gastric tumorigenesis. Overall, we proposed that galectin-3 could be served as a potential target by regulation of WNT and STAT3 signaling for the prevention and/or therapy of gastric cancer.