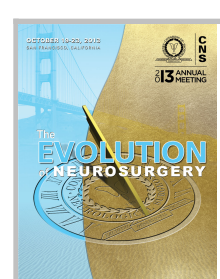


# REIC/Dkk-3, One of Dickkopf (Dkk) Family Members, Contributes to the Anti-tumor Effects in Glioblastoma Through Regulation of Both Wnt Signal Pathways

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## Introduction

Glioblastoma multiforme (GBM) is a lethal primary brain tumor. Whether adenovirus-mediated REIC/Dkk-3 (Ad-REIC) inhibits the proliferation of these cells and how REIC/Dkk-3 protein regulates the Wnt signaling pathway remain to be elucidated. To verify the mechanisms underlying these effects we focused on the regulation by REIC/Dkk-3 protein on the interaction between the Wnt proteins Wnt3a and Wnt5a and their co-receptors LRP6 and ROR2 and examined the Wnt signal downstream cascade.

## Methods

We used U87MG, U251MG, and TGB-111 cells and a murine U87MG cell xenograft model to compare the anti-tumor effects of Ad-REIC and Ad-LacZ. We analyzed the expression of Wnt proteins and its co-receptors by western blot and quantitative RT-PCR. Their interaction was examined by the immunoprecipitate and the activities of downstream cascade were examined by pull-down assay.

## Results

Ad-REIC exerted anti-tumor effects in GBM cells and mice xenograft models. Notably, Wnt3a and Wnt5a interacted with both the co-receptors LRP6 and ROR2 in Ad-LacZ treated cells. Interestingly, the binding of Wnt3a to LRP6 and of Wnt5a to ROR2 was preferentially inhibited by REIC/Dkk3 in Ad-REIC treated cells. In the Wnt signal downstream,  $\beta$ -catenin but not Rac1 was reduced and RhoA activation was inhibited, while JNK and c-Jun were activated. This suggests that the regulation by REIC/Dkk-3 of both canonical and non-canonical Wnt signaling pathways upstream affects functional molecules downstream, thereby exerting anti-tumor effects in GBM.

## Conclusions

Ad-REIC gene therapy may have promise for treating GBM.

## Learning Objectives

By the conclusion of this session, participants should be able to identify that Ad-REIC gene therapy may have promise for treating GBM through Ad-REIC exerted anti-tumor effects in GBM.

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