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REACTIVATION OF APOPTOSIS AS A POTENTIAL THERAPEUTIC TARGET FOR DESMOID TUMORS WITH CTNNB1 S45F MUTATION

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BACKGROUND: Desmoid tumors (DTs) are rare mesenchymal lesions with a high rate of local recurrence. Their common feature is a deregulated WNT pathway, mainly caused by gain-of-function mutations in exon 3 of the *CTNNB1* gene (encoding for β-catenin), resulting in nuclear accumulation of β-catenin. Even though it is controversial, several studies have shown that the mutation S45F strongly correlates with increased propensity for desmoid recurrence. Therefore, it is important to investigate the differences between these two genetic alterations in order to potentially provide targets for novel molecular therapies.

OBJECTIVE: To extensively investigate molecular driving forces behind the differences between the *CTNNB1* S45F and T41A mutations in DTs.

METHODS: To further evaluate the differences between CTNNB1 T41A and S45F mutation, we conducted a gene array assay including 16 desmoid tissues with *CTNBB1* T41A mutation and 14 desmoid tissues with a S45F mutation in the β-catenin gene. The gene array was validated in DT tissues and cell strains using qRT-PCR. As an artificial system, we also transfected mutated β-catenin genes into normal embryonic cells (293T cells) to recapitulate the biology observed in desmoid cells. The ability of inducing apoptosis between the T41A and S45F mutated/transfected cells were assessed via flow cytometry analysis after doxorubicin treatment.

RESULTS: Our results showed that the difference between the *CTNNB1* T41A and S45F mutations is not caused by a simple mutation-driven selected degradation. Our gene array analysis showed that proapoptotic genes are downregulated and anti-apoptotic genes are upregulated in the cells with the S45F mutation when compared to the T41A mutation.

Moreover, we showed that there is no significant induction of apoptosis in the S45F mutated desmoid cell strains or in the transfected 293T cells when compared to the T41A mutated/transfected cells.

CONCLUSION: Our findings suggest that apoptosis is downregulated in desmoid tumors harboring the *CTNNB1* S45F mutation, and that cells with the *CTNNB1* S45F mutation are less able than T41A mutated cells to undergo apoptosis after doxorubicin treatment. The impairment of apoptosis appears to be specific to the *CTNNB1* S45F mutation and not to desmoid tumors *per se*.