The Tyrosine Kinase Receptor RET Interacts \textit{in Vivo} with Aryl Hydrocarbon Receptor-Interacting Protein to Alter Survivin Availability

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\textbf{ABSTRACT}

\textbf{Context:} RET is a tyrosine kinase transmembrane receptor expressed in two main alternative isoforms: RET9 and RET51. RET transduces a positive signal leading to survival, differentiation, or migration in the presence of its ligand ©FN Nonstandard abbreviations (such as GDNF) must be used more than twice to be retained in abstract. Text is treated separately. Glial cell line-derived neurotrophic factor, whereas in its absence a proapoptotic fragment that initiates a negative signaling for apoptosis is generated. The signal transduction mechanisms leading to apoptosis are still unclear.

\textbf{Objective:} To shed light on the mechanisms of RET-induced apoptosis, we searched for novel interactors of RET51.

\textbf{Design:} The "split ubiquitin yeast two-hybrid system" was used with RET51 as bait against a human brain expression library.

\textbf{Results:} We identified aryl hydrocarbon receptor-interacting protein (AIP), a cochaperone recently found mutated in pituitary adenoma patients, as a novel interactor of RET. We showed that RET interacts specifically with AIP both in mammalian cell lines and \textit{in vivo} in the pituitary gland, regardless of the presence of pituitary adenoma-specific mutations. AIP and RET genes were sequenced in 28 pituitary adenoma, but no relevant mutations were found. In addition, we identified the proapoptotic domain of RET as responsible for the interaction with AIP. Finally, we demonstrated that the AIP-RET interaction does not require RET kinase activity or kinase-dependent signal transduction and that it prevents the formation of the AIP-survivin complex.

\textbf{Conclusions:} The identification of the AIP-RET complex represents a starting point to study key cellular processes involved in RET-induced apoptosis.

Hypoglycemia from \textit{IGF2} Overexpression Associated with Activation of Fetal Promoters and Loss of Imprinting in a Metastatic Hemangiopericytoma

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\textbf{ABSTRACT}

\textbf{Context:} The mechanism of \textit{IGF2} overexpression in non-islet-cell tumor hypoglycemia is not understood.

\textbf{Objective:} We investigated the imprinting control and promoter usage for \textit{IGF2} expression to identify a mechanism for increased \textit{IGF-II} production in non-islet-cell tumor hypoglycemia.

\textbf{Patient and Methods:} A patient with metastatic hemangiopericytoma was studied. Tissue from the original hemangiopericytoma, metastatic tumor, and uninvolved liver was analyzed for \textit{IGF-II} immunohistochemistry. \textit{IGF2}, a paternally imprinted gene, shares a control region with maternally imprinted \textit{H19}, a putative tumor suppressor. \textit{IGF-II} and \textit{H19} mRNA expression was compared in metastatic tumor and uninvolved liver by quantitative RT-PCR. Imprinting of \textit{IGF2/H19} genes and \textit{IGF2} promoter usage in metastatic tumor was investigated by RT-PCR and sequence analysis, and the methylation pattern in the \textit{IGF2/H19} imprinting control region was analyzed.

\textbf{Results:} \textit{IGF-II} protein expression was increased in metastatic tumor vs. uninvolved liver and original tumor. In the metastatic tumor, \textit{IGF-II} mRNA was increased 60-fold, but \textit{H19} mRNA was comparable to uninvolved liver; loss of imprinting of \textit{IGF2}, but not \textit{H19}, was identified; no major change in methylation of the \textit{IGF2/H19} imprinting control regions was observed; and transcripts from four different \textit{IGF2} promoters were detected, compared to two in uninvolved liver.

\textbf{Conclusions:} \textit{IGF2} overexpression, newly acquired in the metastatic tumor, was associated with loss of \textit{IGF2} gene imprinting and different promoter usage. The imprinting control mechanism governing the \textit{IGF2/H19} locus was intact, as evidenced by normal levels of \textit{H19}, maintenance of \textit{H19} imprinting, and no major change in methylation of the imprinting control regions.