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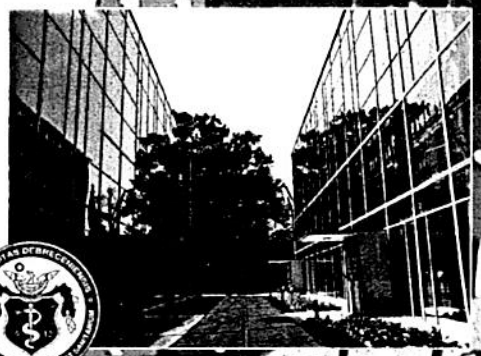

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P14 The p53/YY1/FOXO3a transcriptional complex regulates SDF-1 gene expression in pancreatic beta-cells

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Type 1 diabetes (T1D) is a multifactorial disease characterized by hypoinsulinemia caused by a deficiency of pancreatic beta-cells. Injury of beta-cells resulting from glucotoxicity and cytokine actions during diabetes, induces SDF-1 gene expression in beta-cells. The *de novo* synthesized SDF-1 causes autocrine production of SDF-1 by pancreatic beta-cells and paracrine activation of GLP-1 production by pancreatic alpha-cells. Thus, SDF-1 promotes beta-cell survival and GLP-1 stimulates beta-cell proliferation. Since factors involved in the control of beta-cell growth and survival could provide new approaches for the treatment of T1D in its early stages, we initiated the investigation of molecular mechanisms that regulate gene expression of SDF-1, a potential beta-cell growth factor.

Using the ALGGEN PROMO database, we identified in the SDF-1 promoter potential transcription factor-binding sites for p53, YY1 and FOXO3a. Super-shift analysis revealed that p53, YY1 and FOXO3a were present in nucleoprotein complexes formed between the SDF-1 promoter and pancreatic beta-cell nuclear proteins. *In vivo* chromatin immunoprecipitation (ChIP) analysis confirmed these results. Co-immunoprecipitation (Co-IP) with an antibody raised against p53 revealed that p53 interacts with YY1 and FOXO3a, whereas Co-IP analysis using an YY1 antibody showed that YY1 and FOXO3a are interacting partners in pancreatic beta-cells. We also observed that two predicted YY1 motifs in the SDF-1 promoter overlap with a potential Kozak sequence.

This study shows for the first time that p53, YY1 and FOXO3a are capable of binding to the SDF-1 promoter sequence. We suggest that as a result of the observed binding to the SDF-1 promoter, these transcription factors could be involved in the regulation of SDF-1 gene expression. Our investigation revealed a novel interaction between YY1 and FOXO3a. Also, we confirmed the interaction between p53 and YY1 and the interaction of p53 and FOXO3a in pancreatic beta-cells. Our results demonstrated that all three transcription factors interact with each other, indicating that p53, YY1 and FOXO3a probably form a multi-protein transcription complex that regulates SDF-1 gene expression. Further analysis will define the influence of the p53/YY1/FOXO3a-containing transcriptional complex on SDF-1 gene expression.