**SL-06**

# REGULATION OF PANCREATIC ENDOCRINE FUNCTION BY ACTIVATING SIGNAL COINTEGRATOR-2

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Activating signal cointegrator-2 (ASC-2) is a transcriptional coactivator of many nuclear receptors (NRs) and other transcription factors, and contains two NR-interacting LXXLL motifs (NR boxes). In the pancreas, ASC-2 is expressed only in the endocrine cells of the islets of Langerhans, but not in the exocrine cells. Thus we examined the potential role of ASC-2 in insulin secretion from pancreatic $\beta$-cells. Overexpressed ASC-2 increased glucose-elicited insulin secretion, whereas insulin secretion was decreased in islets from ASC-2+/− mice. DN1 and DN2 are two dominant negative fragments of ASC-2 that contain the NR box 1 and 2, respectively, and block the interactions of cognate NRs with the endogenous ASC-2. Primary rat islets ectopically expressing DN1 or DN2 exhibited decreased insulin secretion. Furthermore, relative to wild type, ASC-2+/− mice showed reduced islet mass and number, which correlated with increased apoptosis and decreased proliferation of ASC-2+/− islets. These results suggest that ASC-2 regulates insulin secretion and $\beta$-cell survival, and that the regulatory role of ASC-2 in insulin secretion appears to involve, at least in part, its interaction with NRs via its two NR boxes.

**Key Words:** ASC-2, Coactivator, Pancreas, Diabetes, Insulin secretion