

P018 Re-inventing the operon: identification of a novel mechanism of transcription regulation in beta cells
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GPR40 and GPR41 are G-protein coupled receptors encoded by adjacent genes that are expressed selectively in pancreatic beta cells. GPR40 is activated by long-chain fatty acids (LCFA) and is implicated in LCFA-dependent insulin secretion. GPR41 is activated by short-chain fatty acids; its function is unknown. The aim of our study was to characterize mechanisms controlling the cell-specific expression of these genes. We showed that expression of the GPR40 gene is controlled in large part by evolutionarily conserved enhancer and promoter sequences located within 1.1 kb of the transcription start site. Unexpectedly, analysis using reporter gene transfections, Northern blot and 5'-RACE showed that the GPR41 gene appears to lack a dedicated promoter: GPR40 and GPR41 mRNA share the same transcription start site, located at the GPR40 promoter. Thus transcription from the GPR40 promoter generates a bicistronic mRNA containing two separate protein coding regions. Though common in prokaryotes, this "operon" structure represents one of the first reported cases in mammalian cells. This unusual gene structure suggests a possible mechanism for coordinate expression of the proteins, perhaps related to the response of the beta cell to changes in blood levels of fatty acids.