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Meeting abstract

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Specific effects of Lef-1 splice variants on the regulation of gene expression in pancreatic cancer cells

S Jesse*[1], K Giehl[1], A König[2] and A Menke[1]

Address: [1]Universitätsklinikum Ulm, Innere Medizin I, AG Molekulare Zellbiologie, Ulm, Germany and [2]Abteilung für Gastroenterologie und Endocrinologie, Universitätsklinikum Giessen und Marburg, Germany

* Corresponding author

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The lymphoid enhancer factor (Lef-1) belongs to the nuclear transducers of canonical Wnt-signalling in embryogenesis and cancer. Lef-1 acts, in cooperation with beta-catenin, as a context-dependent transcriptional activator or repressor thereby influencing multiple cellular functions such as proliferation, differentiation and migration.

Here we report an increased Lef-1 expression in human pancreatic cancer, which correlates with advanced tumour stages. As demonstrated by RT-PCR analysis, pancreatic carcinoma exhibit two different transcripts present in pancreatic carcinomas. One transcript was identified as the full length Lef-1 (Lef-1 FL), whereas the second, shorter transcript, lacked exon VI (Lef-1 exon VI) compared to the published sequence. Comparative analysis of these two Lef-1 variants revealed different cellular effects after transient expression in pancreatic carcinoma cells. Forced expression of Lef-1 exon VI in pancreatic carcinoma cells inhibited E-cadherin expression and resulted in reduced cellular aggregation and increased cell migration compared to cells expressing full length Lef-1. Expression of Lef-1 FL, but not the newly identified Lef-1 exon VI, induced expression of the cell cycle regulating proteins c-myc and cyclin D1 and resulted in enhanced cell proliferation.

Thus, our findings implicate that expression of alternatively spliced isoforms of Lef-1 are involved in the determination of proliferative or migratory characteristics of pancreatic carcinoma cells.