

P010 Leukotriene D₄ Induces TCF/LEF Activation and Association of β -catenin with Bcl-2 in Intestinal Epithelial Cells

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The inflammatory mediator leukotriene D₄ (LTD₄) is present at high levels in many inflammatory conditions. We have previously shown that LTD₄ induces up-regulation of β -catenin, as well as other proteins which can influence survival and proliferation in intestinal epithelial cells. We demonstrate here that following LTD₄ stimulation, β -catenin is translocated to the nucleus triggering the transcriptional activity of the TCF/LEF family of transcription factors. These events were dependent on phosphoinositide-3-kinase (PI-3 kinase) activation and GSK-3 β inhibition. We also report that free β -catenin can translocate to mitochondria upon LTD₄ stimulation and associate with the cell survival protein Bcl-2. The effects of the interaction between these two proteins could also be demonstrated, (1) Bcl-2 over-expression leads to enhanced TCF/LEF promoter activity and (2) high β -catenin levels counteract mitochondrial apoptosis. Our data suggest that, similar to Wnt signalling, LTD₄ increases free β -catenin via inactivation of GSK-3 β , followed by the initiation of TCF/LEF transcriptional activity. Also, this Wnt-like signalling affects cell survival in a positive, previously unknown manner by permitting the association of Bcl-2 and β -catenin at the mitochondria. Together with previous findings this work further delineates the crossing point between inflammation and carcinogenesis.