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"β-CATENIN SUPPORTS p210 BCR-ABL-MEDIATED TRANSCRIPTION, BUT NOT TRANSFORMATION AND DRUG RESISTANCE, IN MURINE MYELOBLASTOID PROGENITOR CELLS"

by

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2 P.M.
ICPH Auditorium (225 Warren Street)

ABSTRACT

The presence and aberrant kinase activity of the p210 variant of the chimeric, oncogenic protein BCR-Abl is most commonly associated with chronic myelogenous leukemia (CML). This clonal malignancy relies on several constitutively active pathways which allow deregulation of the growth and maintenance of progenitor cells and, thus, the disease state. One direct substrate of p210 BCR-Abl implicated in disease progression is β-catenin. This protein has diverse roles within the cell but it is the transcriptionally inactive form, and downregulation of the molecule, that have emerged as targets of research interest in CML β-catenin is known canonically as a molecular anchor to the extracellular matrix. However, upon phosphorylation, it is freed from this function and has the potential to become a transcription factor with multiple transcriptional targets. Similarly, to other transcription factors, the stability, activity, and turnover rate of β-catenin are all governed by phosphorylation dynamics. Previous research from our lab and others has found specific sites on β -catenin which are direct targets of p210 BCR-Abl kinase activity, and have been found to affect the accumulation of β-catenin within the cell. Due to these findings, this current research has focused on the possibility that the β-catenin pathway may govern disease progression in CML. To examine this possibility, we excised the native β-catenin gene from the murine myeloblastoid cell line 32Dcl3 using the Cas-9 endonuclease while subsequently introducing p210 BCR-Abl. Data showed that in the absence of β-catenin expression, cell growth and migration in these cells were affected, but not in a BCR-Abl-dependent manner. Our analysis of the β-catenin and p210 BCR-Abl interaction in these cells also did not support our hypothesis that loss of this interaction may contribute to acquired resistance in CML. Data from real-time PCR studies determined that p210 BCR-Abl may be regulating some, but not all of its transcriptional targets in a β-catenin-dependent manner. A compensatory mechanism involving γ-catenin may account for some of the disparate observations. Collectively, these observations suggest that β-catenin may contribute to some, but not all, p210 BCR-Abl-mediated activities in myeloid progenitor cells, and that this interaction may be relevant to some aspects of CML progression.