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Molecular Analysis of p170, a Central Component of eIF-3, in Cell Growth and Transformation

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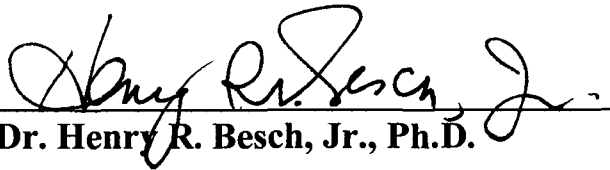
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ABSTRACT

p170 is a critical component of the largest translation initiation factor 3, eIF-3. Previous results from this and other laboratories demonstrated that the expression level of p170 was dramatically increased in many human cancer tissues and cell lines, particularly in lung cancer cells. The goal of my thesis project is to address the role of p170 in malignant cell growth. To do this, I have successfully introduced an anti-sense p170 cDNA construct into a human lung cancer cell line (H1299) that expresses high levels of p170. Forced reduction of p170 expression in a number of isolated clones was confirmed by immunoblotting analysis with a specific anti-p170 antibody. Interestingly, my results demonstrate that human lung cancer cells with down-regulated p170 expression display a significant decrease in cell proliferation rate and reduced plating or colony formation efficiency. This observation suggests a direct correlation between p170 protein levels and cell growth as well as survival. Moreover, it was found that decreased p170 expression causes reversion of the cell transformation phenotype, as indicated by reduced anchorage-independent cell growth in soft agar. These results suggest that p170 plays an important role in promoting cell growth, that abnormal over-expression of p170 may be a cause for the initiation of lung cancer development, and that p170 may be a useful target for pharmaceutical intervention of malignant cell growth in human lung cancer patients. The successful downregulation of the excess amount of p170 protein using the antisense approach and partial reversion of the transformed

phenotype of H1299 cells encourage a potential application of this technique in the clinical treatment of human lung cancers.

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