Amplification of Mouse Chromosome 1 in Lung Adenocarcinoma Cell Strains

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Adenocarcinoma is increasing in incidence in the United States, however, the difficulty in obtaining lung cancer families and representative samples of the various stages of the disease have lead to the study of mouse models. We used Spectral Karyotyping, mapping with fluorescently labeled genomic clones (FISH) and comparative genomic hybridization (CGH) on a BAC array, expression array and real time PCR to analyze the genetic changes in 15 primary mouse lung adenocarcinomas and 9 pairs of high and low invasive tumor cell strains. Spectral Karyotyping analysis demonstrated that the duplication of chromosome 1 was associated with the ability of cells to invade a gel matrix. Mapping with FISH and CGH array further narrowed the minimum region of duplication of chromosome 1 to 71 to 82 centimorgans (cM) as well as three deleted regions from 67-69 cM, 84-84 cM and 100-110 cM. Expression array analysis and validation by real time PCR demonstrated an increased copy number and expression of SKD1, tubulin alpha 4, two nuclear kinases, NUCKS and DYRK, and vacuolar protein sorting 4B in the invasive cell line pairs. Western blot analysis of NUCKS showed increased protein levels in invasive compared to non-invasive cell strains. The amplified copy number and expression of tubulin alpha 4, NUCKS and DYRK3, vacuolar protein sorting 4B, and ELK 4 (involved in epithelial electrolyte transport), were associated with the ability of cells to invade a gel matrix. Increased expression of tubulin alpha 4 is associated with cell movement and mitosis. DYRK3 expression is associated with progenitor cell lineage and has been found to inhibit programmed cell death. The NUCKS protein is expressed in all adult and fetal cell types and has homology to the high mobility group proteins and has an E2F1 binding site. NUCKS is over-expressed in lung, breast and ovarian cell lines. We have demonstrated amplification of expression and copy number of NUCKS in invasive mouse lung cell strains. Decreased expression of genes within the deleted regions included, procollagen III α1 (col3α1), procollagen V α2 (col5α2), protein tyrosine phosphatase receptor type C (ptprc), chemokine (C-X-C) receptor 4 (cxcr4), and Fc receptor IgG low affinity 11b (fcgrba). The alteration of the same linkage groups in mouse and human lung adenocarcinoma indicates that the mouse is a valid model for human lung adenocarcinoma. The region of duplication of chromosomes 1 contain putative susceptibility loci for mouse lung cancer. The homologous linkage groups on human chromosomes 1q32-41 are altered in invasive human lung cancer. Increased copy number and expression of the genes in chromosome 1 may play a functional role in lung cancer development and may aid in the identification of mouse and human lung cancer susceptibility genes.

*The first two authors shared equally in the work.

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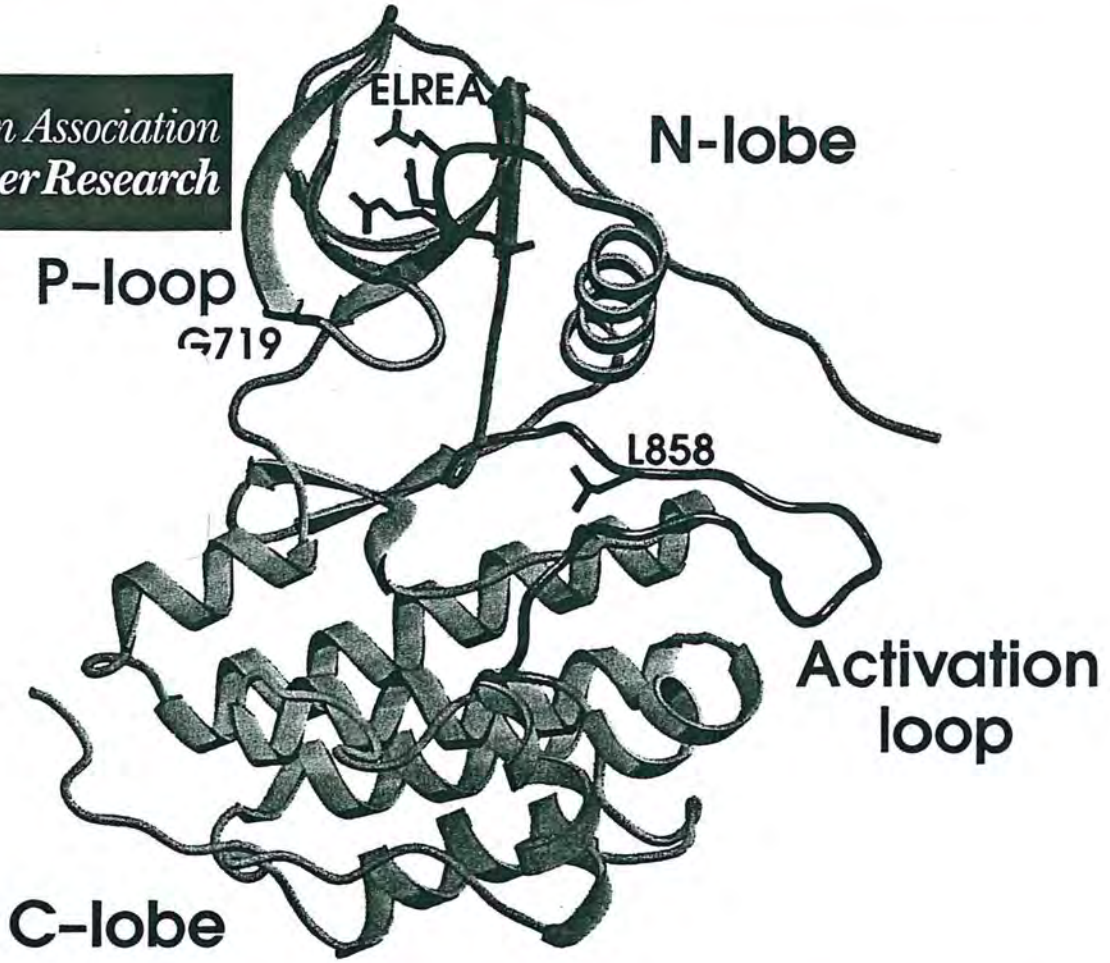

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