Title: Cigarette smoke extract induces activity of the transposable element LINE1 in primary human lung fibroblasts

Body: Introduction: Cigarette smoke causes cell proliferation disorders, including lung cancer and emphysema. Although approximately 40% of lung cancers are associated with p53 mutations, the major part (60%) is of unknown etiology. Integration of transposable elements (TE) in or nearby cell cycle control genes may disrupt the cell cycle and lead to uncontrolled proliferation. This may lead to loss of lung tissue (emphysema), to hyperplasia or the development of tumors. Objective: To assess the effect of cigarette smoke extract (CSE) on the expression and transposition of LINE1 (L1), a human TE present in primary human lung fibroblasts. The L1 open reading frame (ORF)-2 protein was detected using immunoblot-analysis (Western). CSE was used as a 1:10 dilution from a solution containing the smoke equivalent of 1 cigarette/25 ml. Results: Primary fibroblast lines (n=8) were grown in RMPI without and with CSE for 10, 30, 60, 90 and 120 minutes. Resting cells did not express detectable levels of L1-ORF2. CSE induced a biphasic L1-ORF2 expression pattern: an immediate early maximum at 10-30 minutes and a second maximum after 120 minutes. This coincided with a complete inhibition of fibro-proliferation. Conclusions: CSE induces the expression of L1-ORF2, a marker for TE activity. Implications: The increased expression of L1-ORF2 implies an overall increased activity of TE, since the L1-transposition machinery is also used by other mobile elements. Uncontrolled transposition of TE may cause gene damage or alteration. The involvement of TE in smoking-induced proliferation-disorders should be envisaged to understand the heterogeneity observed in lung cancers and emphysema.