# Oncogenic Fusion Gene CD74-NRG1 Confers Cancer Stem Cell-like Properties in Lung Cancer through a IGF2 Autocrine/Paracrine Circuit.

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**Abstract**

The CD74-Neuregulin1 (NRG1) fusion gene was recently identified in invasive mucinous adenocarcinoma of the lung, a malignant type of the lung adenocarcinomas, and is considered to be a new driver gene aberration. However, pathogenic functions of the CD74-NRG1 fusion gene have not yet been understood, and it is unknown whether the driver gene contributes to cancer stem cells (CSCs). Here, we show that expression of the CD74-NRG1 fusion gene induces CSC properties. Expression of CD74-NRG1 facilitated sphere formation of not only cancer cells but also non-cancerous lung epithelial cells. By using a limiting dilution assay in xenograft model, we showed that expression of CD74-NRG1 fusion gene enhances tumor initiating ability. We found that expression of CD74-NRG1 stimulates phosphorylation of ErbB2/3 and activates phosphatidyl inositol 3-kinase (PI3K)/Akt/NF-?B signaling pathway. Furthermore, we found that secreted insulin-like growth factor 2 (IGF2) levels were increased and phosphorylation levels of IGF1 receptor (IGF1R), the receptor for IGF2, were enhanced in a NF-?B activity dependent manner in cells expressing CD74-NRG1. These findings suggest that the CD74-NRG1-stimulated NF-?B activity induces IGF2 autocrine/paracrine loop. In addition, CD74-NRG1 fusion gene-induced tumor sphere formation was suppressed by treatment with inhibitors of ErbB2, PI3K or NF-?B or anti-IGF2 antibody. We thus provide evidence that the CD74-NRG1 fusion protein may not only act as a driver for tumor development but also initiate and maintain CSCs. Inhibition of ErbB/PI3K/Akt/NF-?B signaling pathway or secreted IGF2 are promising therapeutic strategies for CD74-NRG1 fusion positive cancers.

Funding: no