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IL-11: a novel diagnostic biomarker with possible effects in lung adenocarcinoma

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Introduction

Interleukin-11 (IL-11) is a member of the IL6-type of cytokines, which are related to tumour development and progression in several types of cancer. IL-11 activates signalling pathways such as JAK/STAT, PI3K or RAS/ERK, triggered by their common receptor subunit, GP130. Previous findings in our laboratory showed that IL-11 was overexpressed in bronchoalveolar lavage fluid of patients with lung adenocarcinoma compared to non-cancer controls and other histological subtypes of lung cancer, and it could be useful as a diagnosis biomarker for this disease. However, the role of IL-11 in lung cancer has been poorly understood. We aim to define the role of IL-11 in the tumorigenesis of the lung adenocarcinoma, and to elucidate whether this protein could be used as a new therapeutic target.

Material and Methods

IL-11 and IL-11 receptor alpha (IL-11RA) expression were determined in lung adenocarcinoma cell lines and patient-derived xenograft models. In the same cell lines, the activation of JAK/STAT, MEK/ERK and PI3K signalling pathways were analyzed by Western Blot after treatment with 50ng/ml of recombinant human IL-11 (rhIL-11). Furthermore, several lung adenocarcinoma cell lines were transfected to overexpress IL-11 or IL11RA and infected to silence IL-11 using CRIPR/Cas9 technology. With these cell lines generated, different tumorigenic surrogates assays, such as growth curves, clonability, soft-agar, migration and xenografts assays, were made to determine the tumorigenic effects of IL-11 *in vitro* and *in vivo*.

Results

Different pathways with implications in several types of cancer were activated in adenocarcinoma cell lines after IL-11 treatment. However, only STAT3 and especially STAT1 were differentially activated in those cell lines overexpressing IL-11RA. Furthermore, overexpression of IL-11RA and stimulation with rhIL-11 slightly increased the tumorigenic properties *in vitro*, whereas IL-11 overexpression did not. However, *in vivo*, the overexpression of IL-11 resulted in a further increase in the growth of tumors. Finally, IL-11 silencing diminished the tumor properties *in vitro* and *in vivo*.

Conclusions

1. IL-11 activates the JAK/STAT pathway and exerts pro-oncogenic effects in lung adenocarcinoma cell lines.
2. IL-11 silencing diminished the oncogenic properties of the cells *in vitro* and *in vivo.* This protein could be used as a therapeutic target for lung adenocarcinoma patients. Future experiments aim to elucidate this possible role will be performed.
3. IL-11 overexpression/silencing had more clear effects *in vivo* and this could be because of tumor microenvironment involvement. Ongoing experiments have being performed to elucidate this approach.