Highly Sensitive and Selective Anti-cancer Effect by Conjugated HA-Cisplatin in Non-small Cell Lung Cancer Overexpressed with CD44

Yu Hua Quan¹, Byungji Kim², Ji-Ho Park², Yeonho Choi¹,³, Young Ho Choi¹, Hyun Koo Kim¹
Department of Thoracic and Cardiovascular Surgery, Korea University College of Medicine, Seoul, 152-703, Korea, kimhyunkoo@korea.ac.kr

ABSTRACT SUMMARY
In spite of severe side effects, chemotherapy is widely used as a major anticancer treatment in non-small cell lung cancer (NSCLC). HA polymers have become a topic of interest for developing sustained drug delivery systems of peptide and protein drugs in subcutaneous formulations. Based on our experimental results, we strongly believe that HA-cisplatin conjugate is a potential anti-cancer chemotherapeutic agent, which targets CD44 overexpression in NSCLC, with minimal side effects and high therapeutic properties.

INTRODUCTION
Lung cancer is the leading cause of cancer-related deaths worldwide. The majority of patients with lung cancer have non-small cell lung cancer (NSCLC). In order to enhance the therapeutic properties and reduce side effects, enormous efforts have been devoted to direct anticancer agents specifically to tumor tissues by the use of nanoparticles, or cancer cell marker attached drugs. However, cell-specific chemotherapy is still in its infancy and is not applicable to all types of cancers due to the complexity of the cancer occurrence and progress. In this study, we demonstrate that hyaluronan (HA)-conjugated cisplatin has highly selective and sensitive anticancer effects in NSCLC cells that overexpress the trans-membrane receptor, CD44, as HA is a specific ligand for CD44(1, 2).

EXPERIMENTAL METHODS
A CD44 expressing cell-targeted pro-drug was developed for the anti-cancer drug cisplatin, using hyaluronic acid (HA) as the drug carrier. We selected lung cancer cell line and investigated the CD44 expression by confocal and western blotting. The conjugated HA-cisplatin nanogel was treated to human non-small cell lung cancer cell line (H1299, A549) and human normal lung cell line (HFL-1) measured the effects in cell proliferation, motility, and invasiveness by MTT assay, migration assay, invasion assay. We also investigated the anti-cancer effects of HA-cisplatin nanogel in H1299 cell line, whether inhibited by free HA and CD44 monoclonal antibody.

RESULTS AND DISCUSSION
In proliferation experiments, HA-conjugated cisplatin showed dramatic cell viability decreases (from 100 % to 42.31%) in H1299 cells, which overexpress CD44, whereas no such change was observed in A549 and HFL-1, which have little to no expression of CD44. More importantly, conjugation with HA decreased the dosage concentration of cisplatin by 50 fold for both cytotoxic and anti-metastatic effects. In addition, HA-cisplatin conjugate treatment selectively decreased migration (from 100% to 7.8%) and invasiveness (from 100% to 21.4%, respectively) of H1299.
CONCLUSION

We clearly demonstrate that HA-CD44 interaction contributes to selective and sensitive anti-cancer effects of HA-cisplatin conjugate in CD44-overexpression NSCLC cells. Despite the in vitro nature of this investigation, the results demonstrated interesting anti-proliferative, pro-apoptotic, and anti-metastatic activities which suggest HA-cisplatin as a promising candidate in the treatment of NSCLC.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government (MEST) (No: 2012012166)

REFERENCES
