Göteborg, 2019

Small intestinal neuroendocrine tumours

Disease models, tumour development, and remedy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 28 mars kl. 9.00.

av **Tobias Hofving**

Fakultetsopponent: Prof. Eva Tiensuu Janson, MD

Uppsala universitet

Avhandlingen baseras på följande delarbeten

I. **Hofving T**, Arvidsson Y, Almobarak B, Inge L, Pfragner R, Persson M, Stenman G, Kristiansson E, Johanson V, Nilsson O. The neuroendocrine phenotype, genomic profile and therapeutic sensitivity of GEPNET cell lines.
Endocrine-Related Cancer, 2018;25(3):367-380

II. **Hofving T***, Karlsson J*, Nilsson O**, Nilsson JA**. H-STS, L-STS, and KRJ-I are not authentic GEPNET cell lines.
Nature Genetics; accepted for publication

III. **Hofving T**, Elias E, Inge L, Altiparmak G, Rehammar A, Kristiansson E, Nilsson O*, Arvidsson Y*. *SMAD4* haploinsufficiency in small intestinal neuroendocrine tumours.
Manuscript

IV. **Hofving T**, Sandblom V, Arvidsson Y, Shubbar E, Altiparmak G, Swanpalmer J, Almobarak B, Elf AK, Johanson V, Elias E, Kristiansson E, Forssell-Aronsson E, Nilsson O. ^{177}Lu-octreotate therapy for neuroendocrine tumours is enhanced by Hsp90 inhibition.
Endocrine-Related Cancer, 2019;26(4):437-449

V. **Hofving T**, Liang F, Karlsson J, Yrlid U, Nilsson JA, Nilsson O*, Nilsson LM*. The microenvironment of small intestinal neuroendocrine tumours contains lymphocytes capable of recognition and activation after expansion.
Manuscript

SAHLGRENSKA AKADEMIN
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Abstract

This thesis addressed some of the main challenges in the research of small intestinal neuroendocrine tumours (SINETs). SINETs are malignant neoplasms which at the time of diagnosis often present with distant metastasis. The fact that the tumour disease often present with distant metastasis, and that curative therapeutic options for spread disease do not exist, is deeply troubling. It is therefore of outmost priority to develop such therapies.

In order for preclinical researchers to perform studies that ultimately lead to a cure, we first need to make sure the models we use recapitulate the aspects of the disease we want to study. **Paper I and II** investigated cell lines frequently used for studying gastroenteropancreatic neuroendocrine tumours. We found that several well-studied SINET cell lines were non-authentic. These cell lines consisted of immortalised B lymphocytes and the use of these cell lines may have led to faulty conclusions in a number of published studies. In **paper III** we moved on to investigate the molecular changes that underlie SINET development and progression. We suggested that recurrent hemizygous copy-number alterations played an important role, exemplified by *SMAD4* haploinsufficiency in SINETs. **Paper IV** investigated whether the newly approved ^{177}Lu-octreotate therapy could be potentiated for SINETs using combination therapy. We managed to demonstrate that inhibition of Hsp90 in several SINET models led to a synergistic enhancement of the ^{177}Lu-octreotate therapy to kill SINETs. In **paper V** we investigated SINETs in relation to tumour-infiltrating lymphocytes. In addition to providing a thorough characterisation of immune cell types present in the SINET microenvironment, we demonstrated that it is possible to isolate and expand SINET-infiltrating lymphocytes. These expanded lymphocytes could then be activated when challenged with autologous SINET cells. In conclusion, this thesis presents novel findings relating to SINET models, tumour development, and potential remedy.

Keywords: neuroendocrine tumours, tumour models, SMAD4, ^{177}Lu-octreotate therapy, immunotherapy

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