Defining RCE1 and ICMT as Therapeutic Targets in K-RAS–induced Cancer

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ABSTRACT

CAAX proteins, such as the RAS and RHO proteins, are recognized by a specific *CAAX* motif at the carboxyl terminus, which undergoes posttranslational modifications. First, a lipid group is attached to the cysteine (the "*C*") of the *CAAX* motif by farnesyltransferase (FTase) or geranylgeranyltransferase-I (GGTase-I); second, the *–AAX* are removed by RAS converting enzyme 1 (RCE1); and third, the cysteine is methylated by isoprenylcysteine carboxyl methyltransferase (ICMT). These modifications are important for the subcellular localization of the protein and for protein-protein interactions.

Several *CAAX* proteins, including RAS and RHO, are involved in the pathogenesis of cancer. Therefore, much effort has focused on exploring the possibility of inhibiting *CAAX* proteins as an anticancer strategy. One potential strategy would be to inhibit the *CAAX* processing enzymes; FTase, GGTase-I, ICMT or RCE1. Previous studies showed that inactivating *Rce1* and *Icmt* in mouse fibroblasts mislocalized RAS away from the plasma membrane and reduced RAS transformation, but nothing was known about the impact of inhibiting these enzymes on cancer development *in vivo*.

The aim of this thesis was to define the impact of inactivating *Rce1* and *Icmt* on the development of K-RAS–induced cancer and thus validate the *CAAX* processing enzymes RCE1 and ICMT as potential therapeutic targets for cancer treatment.

Cre-*lox*P techniques were used to activate an oncogenic K-RAS allele and inactivate *Rce1* or *Icmt* in hematopoietic cells in mice. Activation of the oncogenic K-RAS allele in hematopoietic cells results in a lethal myeloproliferative disease (MPD) with leukocytosis, splenomegaly and autonomous colony growth of hematopoietic cells.

Surprisingly, inactivation of *Rce1* worsened all the phenotypes of the K-RAS−induced MPD and caused the mice to die earlier. On the contrary, inactivation of *Icmt* inhibited the progression of MPD and reduced splenomegaly and autonomous colony growth. Furthermore, inactivating *Icmt* reduced lung tumor development in a K-RAS induced lung cancer model.

The results indicate that inhibiting RCE1 may not be a good strategy for treating RAS-induced hematological malignancies. ICMT, on the other hand, appears to be a promising therapeutic target, and should be further evaluated for the treatment of both hematological malignancies and solid tumors.

Keywords: RCE1, ICMT, K-RAS, *CAAX* proteins, MPD, lung cancer

ISBN: 978-91-628-7712-5. Göteborg 2009

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Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg,

torsdagen den 30 april 2009, kl. 9.00

av

Annika Wahlström

Fakultetsopponent: Professor Channing J. Der,

University of North Carolina at Chapel Hill, USA

Avhandlingen baseras på följande delarbeten:

I ***Rce1*** **deficiency accelerates the development of K-RAS–induced myeloproliferative disease.**

Annika Wahlström, Briony Cutts, Christin Karlsson, Karin Andersson, Meng Liu, Anna-Karin Sjögren, Birgitta Swolin, Stephen G. Young, Martin Bergö.

Blood. 2007, **109**:763–768.

II **Inactivating** ***Icmt*** **ameliorates K-RAS–induced myeloproliferative disease.**

Annika Wahlström, Briony Cutts, Meng Liu, Annika Lindskog, Christin Karlsson, Anna-Karin Sjögren, Karin Andersson, Stephen G. Young, Martin Bergö.

Blood. 2008, **112**:1357-1365.

UNIVERSITY OF GOTHENBURG

2009