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

Annika Wahlström

The Wallenberg Laboratory, Department of Molecular and Clinical Medicine, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Sweden, 2009.

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 farnesytransferase (FTase) or geranylgeranyltransferase-I (GGTase-I); second, the –AAAX 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 lcmt 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 lcmt 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-loxP techniques were used to activate an oncogenic K-RAS allele and inactivate Rce1 or lcmt 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 lcmt inhibited the progression of MPD and reduced splenomegaly and autonomous colony growth. Furthermore, inactivating lcmt 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

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Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien 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.

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.