Functional Analysis of CCR4-NOT Complex in Pancreatic β Cell

Final Exam Abstract

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Functional analysis of CCR4-NOT complex in pancreatic β cell
Pancreatic β cells are responsible for production and secretion of insulin in response to increasing blood glucose levels. Therefore, defects in pancreatic β cell function lead to hyperglycemia and diabetes mellitus. While extensive research has focused on signaling, transcriptional, and epigenetic regulation in β cells, how post-transcriptional mechanisms influence the β cell gene expression program is largely unknown. The carbon catabolite repression 4 (CCR4)–negative on TATA-less (NOT) complex (CCR4-NOT complex), a major deadenylase conserved in eukaryotes, catalyzes mRNA deadenylation which is the rate limiting step in mRNA decay pathway. The CCR4-NOT complex has been implicated in the development of metabolic diseases. However, whether the CCR4-NOT complex affects β cell function is not addressed. In this thesis, I aim to understand the importance of posttranscriptional regulation in β cells by generating mice lacking the Cnot3 gene, which encodes an essential CCR4-NOT complex subunit, in β cells. Suppression of CNOT3 in β cells caused β cell dysfunction and diabetes. This was associated with the decreased expression of β cellspecific genes and increased expression of genes specifically repressed in β cells, called "β cell disallowed genes". By combining whole transcriptome and proteome analyses and subsequent validations using quantitative PCR (qPCR) and immunoblot analyses, I found that mRNA and protein expression patterns were largely different from normal β cells upon CNOT3 suppression, which was clearly relevant to the observed phenotypes. I also found that some β cell disallowed genes were stabilized in the absence of CNOT3, suggesting that their expression was maintained at low levels under the control of the CCR4-NOT complex. Together, this study uncovered mRNA deadenylation by CCR4-NOT complex as a novel molecular mechanism by which β cell identity and function are regulated.

*Note: OIST Policy Rules and Procedures (extract)

5.3.13.3 Appointment of the Thesis Examination Panel

After receiving the Notice of Intent to Submit a Thesis, the Curriculum and Examinations Committee (CEC) will appoint thesis examiners from within and outside the University, to form a Thesis Examination Panel, as follows:

i. Two Examiners selected from two different working-countries, who are expert in the field of the proposed thesis and external to OIST. The CEC appoints the examiners taking into account nominations provided by the Thesis Supervisor. The CEC is responsible for determining if the nominated examiner is expert in the field of the proposed thesis research, taking into account the publications of the examiner in international peer reviewed journals.
ii. A Chair selected from the OIST faculty members with knowledge OIST standards and regulations concerning PhD thesis examinations.

The Thesis Supervisor is responsible for ensuring that the nominated examiners meet the specified conditions. The Academic Services Section of the Graduate School is responsible for checking that the specified conditions are satisfied. If the conditions are not satisfied, the nomination shall not be submitted to the CEC, and the Supervisor shall be advised on the grounds for declining the examiner and asked to nominate a new examiner by the Academic Services Section.

The CEC may alternatively appoint an examiner who has not been nominated by the Supervisor.