Adenosine-triphosphate-binding cassette transporter-A1 (ABCA1) maintains intracellular cholesterol homeostasis and generates high density lipoprotein (HDL) cholesterol. The maintenance of cholesterol homeostasis in cells is crucial for proper cellular function. Epidemiological studies consistently demonstrate an inverse relationship between HDL levels and cardiovascular disease (CVD), independent of LDL and triglyceride levels.

In this thesis we attempt to identify novel post-transcriptional and post-translational mechanisms that regulate ABCA1 expression and/or function. Prior to translation, ABCA1 protein expression is regulated by non-coding RNA molecules known as microRNAs which bind and inhibit translation of mature mRNA transcripts in the cytoplasm. In this study we used bioinformatic prediction programs to identify potential microRNA regulators of ABCA1. Using reporter constructs, protein expression analysis by immunoblotting, and cholesterol efflux assays, we validated microRNA-145 as a novel repressor of ABCA1 translation. The inhibition of endogenous microRNA-145 in HepG2 cells increased both ABCA1 protein levels and cholesterol efflux activity.

Following translation, numerous post-translational modifications and protein-protein interactions are required for the ABCA1 protein to function properly. In this study we identified palmitoylation as a novel post-translational modifier of ABCA1. The majority of ABCA1-mediated cholesterol efflux and HDL biogenesis occurs at the cell surface. We showed that palmitoylation is a crucial lipid addition for proper ABCA1 plasma membrane localization. We also identified a number of enzymes that mediate the incorporation of radio-labeled palmitate onto ABCA1, and demonstrated that the overexpression of the palmitoyl transferase enzyme DHHC8 increases ABCA1 palmitoylation and cholesterol efflux activity. In this thesis, we have contributed to the understanding of ABCA1 biology by the identification of two novel regulators of ABCA1 expression and/or function.

BIOGRAPHICAL NOTES

M.Sc., Queen’s University, 2003

Current Position: Ph.D. candidate, University of British Columbia

GRADUATE STUDIES

Field of Study: Post-transcriptional regulation of proteins

Courses

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<thead>
<tr>
<th>Code</th>
<th>Course Title</th>
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<tr>
<td>BIOC 509</td>
<td>Membrane Structure and Function</td>
<td>Dr. R. Molday</td>
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<tr>
<td>MEDG 520</td>
<td>Advanced Human Molecular Genetics</td>
<td>Dr. C. Brown</td>
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<td>MEDG 530</td>
<td>Human Genetics</td>
<td>Dr. L. Clarke</td>
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<td>MEDG 545</td>
<td>Current Topics in Medical Genetics Research</td>
<td>Dr. E. Conibear</td>
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<tr>
<td>MEDG 548</td>
<td>Directed Studies</td>
<td>Dr. M. Hayden</td>
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AWARDS

The Pacific Century Graduate Scholarship, UBC (2007-2008)
University Graduate Fellowship, UBC (2007-2008)
UBC Graduate Entrance Scholarship, UBC (2005)
Queen’s Graduate Fellowship, Queen’s (2000)
Queen’s Graduate Award, Queen’s (1999-2000)
Professor CFA Culling Award, UBC (1998)
UBC Scholarship, UBC (1997)

SELECTED PUBLICATIONS

Kang MH, Zhang L, Wijesekara N, Butland S, Bhattacharjee A, Hayden MR. Regulation of ABCA1 Protein Expression and Efflux Function in Hepatic and Pancreatic Cells by miR-145. (2012) Manuscript in preparation. (These authors contributed equally to this work)


SELECTED PRESENTATIONS


SUPERVISORY COMMITTEE

Dr Michael R Hayden (Research Supervisor), Medical Genetics
Dr Elizabeth Conibear, Medical Genetics
Dr Robert Molday, Biochemistry
Dr Cheryl Wellington, Pathology and Laboratory Medicine

THE UNIVERSITY OF BRITISH COLUMBIA

PROGRAMME

The Final Oral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Medical Genetics)

MARTIN HUBERT KANG

M.Sc., Queen’s University, 2003

Friday, November 2, 2012, 9:00 am
Room 200, Graduate Student Centre
Latecomers will not be admitted

“Post-transcriptional Regulation of ABCA1”

EXAMINING COMMITTEE

Chair:
Dr. Evica Rajcan-Separovic (Pathology and Laboratory Medicine)

Supervisory Committee:
Dr. Michael R. Hayden, Research Supervisor (Medical Genetics – Attending via teleconference)
Dr. Elizabeth Conibear (Medical Genetics)
Dr. Robert Molday (Biochemistry)

University Examiners:
Dr. John Hill (Pathology and Laboratory Medicine)
Dr. Eric Jan (Biochemistry)

External Examiner:
Dr. Arnold von Eckardstein
Institute of Clinical Chemistry
University of Zurich
Zurich, Switzerland