BIOCHEMICAL AND BIOPHYSICAL CHARACTERIZATIONS OF IMMUNOGLOBULIN SUPERFAMILY RECEPTORS NEOGENIN AND L1

Thesis by

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In Partial Fulfillment of the Requirements for the

degree of Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2011

(Defended September 10, 2010)

ACKNOWLEDGEMENTS

I am deeply indebted to my advisor, Professor Pamela J. Björkman, for giving me this great opportunity to explore biochemical research. She has always had confidence in my capability even though I had no prior training in biology. Without her support, I wouldn't have come this far. I am also grateful for her understanding and encouragement when I had difficulties in research or everyday life.

I would like to express the deepest appreciation to my committee chair, Professor Douglas C. Rees, whose guidance and persistent help in these many years made this dissertation possible. I also want to thank my committee members, Professor Aron Kuppermann and Professor Rob Phillips. Aron has always been insightful – he often reminded me of my physical chemistry background with his inspiring questions. Collaboration with Rob and Rob's former graduate student Tristan on the L1 project has been a great experience and I benefited a lot from it.

Dr. Anthony P. West initiated one of the thesis projects before I joined the lab. I want to express my heartfelt gratitude to him for being such a great scientist and a good mentor over the years. I also received plenty of technical advice from many outstanding fellow researchers, including former graduate students Agi Hamburger, Devin Tesar, Adrian Rice, and Joshua Klein, former postdoctoral scholars Drs. Zhiru Jenny Yang, Rich Olson, Tal Arnon, Elizabeth (Libby) Sprague, and Galina Jerdeva. Jenny has been a great friend and mentor since I joined the lab in early 2005 and I feel very fortunate to have shared the many years in the lab with her. Thanks Kathryn (Beth) Huey-Tubman, Rachel Galimidi, Priyanthi Gnanapragasam, and Paola Marcovecchio for being great colleagues and good friends. Discussions with Dr. Zhenfeng Liu at the Rees lab and Dr. Yan Zhang at the Chan lab were always helpful and I want to thank them for that. Dr. Jens Kaiser has been a great resource and extremely fun to talk to.

Special thanks go to Inder Nangiana, Michael Anaya, Dr. Jost Vielmetter, and the Caltech Protein Expression Center for assistance in expression of almost all proteins I ever made, Pavle Nickolovski and the Caltech Molecular Observatory for assistance

with automated crystallization, and former X-ray lab manager Dr. Leonard Thomas for his help with my first X-ray data collection.

Collaboration with Dr. An-Sheng Zhang at the Enns lab at Oregon Health and Sciences University has been pleasant and rewarding. I hope to see more of the iron-regulatory protein story with your never-ending effort.

I also want to express my gratitude to Dr. Ken Brakke, the author of Surface Evolver, for troubleshooting with the simulation script promptly.

I wish to thank Marta Murphy, Lynda Llamas, Dian Buchness, Agnes Tong, Icy Ma, and all other administrative staff for supporting me during the completion of this thesis project.

Last but not least, I would like to thank my husband Yu Liu for his continuous love over the years. Thanks to my adorable 17-month old son Yun-cong Evan Liu for giving me all the smiles. Thanks to my mother, Nanying Liang, who always offers her love and support when I need it most and for being understanding the entire time. I dedicate this work to them.

ABSTRACT

Immunoglobulin (Ig) superfamily receptors function in a wide variety of developmental and metabolic processes. We are particularly interested in characterizing two Ig superfamily receptors neogenin and L1. The first chapter of the thesis gives a brief review of the biological significance of neogenin and L1 and what has been learned in their functions. In Chapter 2, we describe the localization of the hemojuvelin-binding epitope of neogenin to the membrane proximal fifth and sixth fibronectin type III (FNIII) domains, with the sixth FNIII domain contributing the majority of the binding. Chapter 3 presents the crystal structure of this hemojuvelin-binding fragment at 1.8 Å, revealing a nearly linear domain arrangement. Hemojuvelin binding sites have been mapped to one face of the sixth FNIII domain based on sequence alignment between neogenin and DCC (Deleted in Colorectal Cancer), a molecule related to neogenin but does not bind to hemojuvelin. These results should also be informative in understanding the interaction between neogenin and repulsive guidance molecule (RGM), the closest homologue of hemojuvelin. The interaction between neogenin and RGM is known to regulate neuronal survival. Chapter 4, the second part of the thesis, describes our studies of L1-mediated homophilic adhesion using biophysical approaches. We built a basis shape model to describe L1-mediated homophilic adhesion between L1-coated giant unilamellar vesicles and flat substrate. Using confocal microscopy techniques, we were able to reconstruct the three-dimensional shape of an adhered vesicle. We developed an algorithm in order to derive adhesion strength from the configurations of adhered vesicles based on our basis shape model using energy minimization approach.

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