Jan. 31th, 2012 [redacted] [redacted]

BMB Seminar Series 2013

Date: Jan. 24th, 2013

Lecture Title: 'Structure and function of membrane transport proteins'

Lecturer: Ming Zhou

Summary:

Dr. Zhou's lecture focussed on the transport of urea across the cell membrane. The high polarity of urea prevents is free diffusion across the membrane, as such it must be transported. Urea transport is accomplished by UT-B (urea transporter B) whose transport activity is specific to urea and not water, ammonia, or glycerol. Dr. Zhou was interested in studying how UT-B can show high specificity for urea, however low specificity for other small, highly polar molecules such as water. UT-B was shown to have likely resulted from a duplication event due to the presence of two sequences forming pseudosymmetrical folds in its transmembrane domain. This pseudosymmetrical domains associate, generating a channel through the membrane at their interface. A high resolution crystal structure reveals a repeated carbonyl backbone on one side of the channel, each of which is ~3.6 angstroms apart, with highly hydrophobic residues located on the opposite side of the canal. Dr. Zhou presented a model in which a molecule would have to be able to hydrogen bond to two carbonyl groups at a time to pass through the channel, thereby, the two H-bond acceptors on the small molecule would have to be ~6 angstroms apart. This model explains how water and ammonia are occluded from crossing the channel. Lastly, Dr. Zhou described how UT-B is able to sense osmotic pressure differences and respond my modulating the rate of urea transport to maintain homeostasis.

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Date: Feb. 18th, 2013

Lecture Title: 'Extracting iron from hemoglobin by Staphlococcus aureus'

Lecturer: Michael Murphy

Summary:

Dr. Murphy's lecture focused on iron and heme acquisition by *Staphlococcus aureus.* Dr. Murphy described how vaccine development against *S. aureus* has involved the use of IsdA which contains a so called 'NEAT' domain, facilitating heme binding to IsdA. In fact, IsdA enables *S. aureus* to abstract iron from host hemoglobin, contributing to its pathogenicity. Dr. Murphy's discussion of IsdA took a primarily structure-function approach, using X-ray crystallography as a tool to describe how conformations of distal and proximal histidines in the active site modulate heme binding to IsdA. In fact, as demonstrated, rotation of the distal histidine prevented heme binding. I was interested to see that IsdA homologue, IsdB, which facilitates heme transfer across the cell membrane, has a distal methionine rather than a His as is commonly observed in heme binding proteins, however the significance of this evolutionary adaption was not discussed. To measure K_D values for heme binding to IsdA, an assay was described in which IsdA: heme was incubated in the presence of apo-myoglobin. Upon dissociation of heme from IsdA, My-Hb formed, whose concentrations could be assayed over time. It was found that IsdA released heme very slowing, however in the presence of IsdC, the rate of release was increased 10^6x. Further structural discussions revealed how association of IsdA and IsdC and tyrosine alignment resulted in this reduced heme binding.

Dr. Murphy's talk concluded with a discussion of IsdG and IsdI, both of which are heme oxidases which consume dioxygen to catalyze the degradation of heme and subsequent release of iron. Interestingly, crystallographic and NMR data were used to show an atypical 'ruffled' conformation of heme in which electrons were atypically localized over the entire pi-orbital system.

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Date: Mar. 18th, 2013

Lecture Title: 'Beyond the signaling sequence hypothesis: How mRNAs encoding secretory proteins are trafficked and translated in mammalian cells'

Lecturer: Alex Palazzo

Summary:

Dr. Palazzo's lecture focussed on answering the question 'how do cells manage mRNAs'? Dr. Palazzo described how one half to one third of all ribosomes are bound to the rough ER at any given time. As such, it is difficult to observe ribosome activity in the cell without the complicating factors of the ER. In fact, a protocol for separating these ribosomes from the ER was described. Digitonin was used to disrupt the cell membrane leaving the ER and bound ribosomes. mRNA receptors in the rough ER were observed for the mRNA, p180. Over expression of p180 promoted increased association of a specific t-ftz-mRNA with the ER. In contrast, deletion of p180 prevented this association.

A second section of Dr. Palazzo's lecture focused on secreted proteins. A 5' signal sequence coding region (SSCR) on certain mRNAs was shown to direct their translated products for secretion. This SSCR encodes for a highly hydrophobic region of the gene product. Interestingly codons within this SSCR were deficient in adenines. In fact, in frame silent mutations to a codon for the same amino acid, but possessing an adenine disrupted export of the translated protein. Lastly, Dr. Palazzo identified that mRNAs encoding for secreted proteins contain less introns in their 5' ends than the rest of mRNAs, providing another potential identifier for a secreted proteins. However, Dr. Palazzo recognized that this is not always the case as some mRNAs encoding for secreted proteins utilize a splicisome dependent process.

UBC pharmacy special lecture.

Date: Mar. 27th, 2013

Lecture Title: 'Design and selection of glycoside inhibitors: towards therapies for diabetes and influenza'

Lecturer: Dr. Steven Withers

Summary:

Dr. Withers' work focuses on the mechanisms of glycosidases and the rational design of transition state mimics as potential therapeutics. Two systems were discussed. First, Dr. Withers described how human pancreatic amylase is able to catalyze the transglycosylation of the well known inhibitor, acarbose. Inhibition of pancreatic amylase is of specific interest due to its role in the hydrolysis of saccharides. By inhibiting pancreatic amylase, blood glucose levels are lowered due to the reduced availability of glucose, and therefore, is of great interest to diabetes research. Dr. Withers discussed how his lab was able to identify the complex molecule, Montbretin A as a novel inhibitor of human pancreatic amylase in a high through put screen designed to identify inhibitors that undergo transglycosylation like acarbose. Interestingly, montbretin A could be obtained in high yields from a plant that was easily cultivated. Using a murine model, montbretin A showed delayed onset of diabetes.

Secondly, Dr. Withers described his work on the influenza surface protein, neuraminidase. Dr. Withers demonstrated that the electron withdrawing effect of fluoridated transition state analogues trapped an acyl-enzyme intermediate following nucleophilic catalysis by an active site aspartic acid. The efficacy of these noncompetative inhibitors were tested using plaque assays. Results are encouraging and have moved towards clinical trails.

Metcalf, Doris

From: Adam Crowe <adamcro@mail.ubc.ca>
Sent: Thursday, April 11, 2013 4:21 PM
To: Tang, Tina
Subject: BMB seminars
Attachments: Withers 270313.docx; Zhou 240113.docx; Palazzo 180313.docx; Murphy 180213.docx

Categories: Yellow Category

Doris,

Attached are my BMB seminars. I apologize for the tardiness, however i was focused on my comprehensive exam. Also, i know that i am missing quite a few, however the last few months have been my busiest and i was unable to take the time to attend some seminars.

Thanks

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