The Centre for Blood Research Seminar Series

CBR

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Wednesday, April 24th, 2013
LSC 3 - Life Sciences Centre
2350 Health Sciences Mall

12-1pm

"Loss of ER Glycoprotein Quality Control During the Terminal Differentiation of Human Red Blood Cells"

The glycoprotein, Band 3 or anion exchanger 1 (AE1) catalyzes the electro-neutral exchange of chloride and bicarbonate across the red cell membrane and is present at about 1 million copies per cell, similar to Glycophorin A with which it interacts forming the Wright (Wr) blood group antigen. A truncated form of AE1 is expressed in acid-secreting intercalated cells in the kidney (kAE1) where it mediates bicarbonate re-absorption into the blood. Mutations in the *AE1* gene can lead to red cell diseases like Southeast Asian Ovalocytosis (SAO) or hereditary spherocytosis (HS) and kidney diseases like distal renal tubular acidosis (dRTA).

How do these mutations result in disease? Mutations cause AE1 to mis-fold and be retained in the endoplasmic reticulum (ER) by interacting with the chaperone calnexin, a component of the protein quality control system of the cell that binds glycoproteins during their folding in the ER. Disruption of this interaction results in cell surface expression (rescue) of functional dominant but not non-functional recessive dRTA mutants, nor severely mis-folded AE1 SAO. Interestingly, calnexin is selectively lost during the terminal differentiation of CD34+ human progenitor blood cells. This may explain why some mis-folded mutants like AE1 SAO escape quality control and are present in the mature red blood cell of patients. Other mutants like AE1 HS are retained in the ER by additional mechanisms and are likely removed along with the ER during red cell maturation leading to a loss of AE1 in the mature red cell. Thanks to CIHR, CBS, KFC and U of T for financial support.

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