REGIONAL CENTRE FOR BIOTECHNOLOGY

Colloquium

FcRn as a therapeutic target: from subcellular behavior to *in vivo* studies in mice

E Sally Ward Ober, PhD

Paul and Betty Meek-FINA Professor

University of Texas Southwestern Medical Center

Dallas, USA

Friday, September 28, 2012

4:00 pm

Seminar Room

The MHC Class I-related receptor, FcRn, plays a pivotal role in regulating the transport and distribution of IgG in vivo. FcRn-IgG interactions are characterized by marked pH dependence, with relatively tight binding at pH 6.0 that becomes progressively weaker as near neutral pH is approached. This pH dependence allows IgG molecules to interact with FcRn in acidic early endosomes following uptake into cells, followed by recycling/transcytosis and exocytic release at the cell surface.The engineering of IgGs with higher affinity for FcRn is of considerable interest since it can be used to produce antibodies with longer in vivo half-lives, but only if the pH dependence of the interaction is retained. Conversely, engineered IgGs with increased affinity for FcRn at both acidic and near neutral pH can act as potent inhibitors of FcRn. Such engineered antibodies ('Abdegs', for antibodies that enhance IgG degradation) can lower the levels of endogenous IgG. We have recently shown that Abdegs can be used to treat disease in a mouse model of arthritis. Related to targeting FcRn for therapy, it is informative to define which cell types contribute to the functional activity of FcRn in vivo. Towards this goal, we have generated mice harboring a floxed FcRn allele to allow the site specific deletion of FcRn.From the point of view of using antibodies as therapeutics and from a cell biological perspective, it is important to understand how FcRn performs its function as a salvage receptor within cells and at the whole body level. We are therefore using a combination of fluorescence imaging approaches, including single molecule and multifocal plane microscopy, to analyze how FcRn and its IgG cargo traffick within live cells.

E Sally Ward Ober, PhD

Abstract

The MHC Class I-related receptor, FcRn, plays a pivotal role in regulating the transport and distribution of IgG in vivo. FcRn-IgG interactions are characterized by marked pH dependence, with relatively tight binding at pH 6.0 that becomes progressively weaker as near neutral pH is approached. This pH dependence allows IgG molecules to interact with FcRn in acidic early endosomes following uptake into cells, followed by recycling/transcytosis and exocytic release at the cell surface.The engineering of IgGs with higher affinity for FcRn is of considerable interest since it can be used to produce antibodies with longer in vivo half-lives, but only if the pH dependence of the interaction is retained. Conversely, engineered IgGs with increased affinity for FcRn at both acidic and near neutral pH can act as potent inhibitors of FcRn. Such engineered antibodies ('Abdegs', for antibodies that enhance IgG degradation) can lower the levels of endogenous IgG. We have recently shown that Abdegs can be used to treat disease in a mouse model of arthritis. Related to targeting FcRn for therapy, it is informative to define which cell types contribute to the functional activity of FcRn in vivo. Towards this goal, we have generated mice harboring a floxed FcRn allele to allow the site specific deletion of FcRn.From the point of view of using antibodies as therapeutics and from a cell biological perspective, it is important to understand how