HUMAN TECHNOPOLE

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ROLE OF FORCES IN MEMBRANE DYNAMICS AND LIVER TISSUE MORPHOGENESIS

Rab GTPases are key components for the biogenesis, transport and function of cellular membrane organelles. Rab GTPases and their effectors mediate the specificity and directionality of membrane fusion. Membrane tethering factors provide the first level of specificity in recognising a vesicle by its target compartment. EEA1 is a long dimeric coiled-coil tether molecule that is recruited on the early endosome membrane. Upon binding Rab5 to its N-terminus, it undergoes a conformational change from extended to a more flexible “collapsed” state, giving rise to an effective force. Rab5 and EEA1 effectively constitute a novel two-component molecular motor, cyclically converting the free energy of GTP binding and hydrolysis into mechanical work. We are now exploring the role of Rab GTPases and endocytic mechanisms in liver tissue organisation and regeneration. In the liver, hepatocytes are uniquely polarised cells at the interface of sinusoidal endothelial and bile canaliculi networks that transport blood and bile, respectively. In contrast to simple epithelia, where cells have a single apical surface facing the lumen of organs, hepatocytes exhibit a multipolar (biaxial) organisation, i.e. have multiple apical and basal domains, and their apical surface grows anisotropically to create the narrow tubes of the bile canaliculi and their three-dimensional organisation. By studying bile canalicular network morphogenesis in hepatoblasts in vitro, we discovered that such anisotropic growth is due to the generation of apical protrusions along the tight junction belt that connect the opposed apical surfaces of hepatocytes. These protrusions form a pattern reminiscent of the bulkheads of boats; hence, we call them “apical bulkheads”. The apical bulkheads are under tension and, thus, are structural elements which can provide mechanical stability to the elongating bile canalicular lumen under inner pressure. The small GTPase Rab35 is required to form apical bulkheads and bile canaliculi. Our recent results suggest the existence of a mechano-sensing and -transduction mechanism whereby mechanical alterations of bile canaliculi are sensed and regulate hepatocyte fate.