KHOREN PONSIN, McGill University

Mathematical Modeling of Cellular Phagocytosis During Embryogenesis of the Urogenital System

During embryonic development of the urogenital system in mice, apoptosis plays a crucial role in removing a temporal structure called the Common Nephric Duct (CND), a necessary step to connect the ureter to the bladder epithelium. Experimental data suggest that apoptotic cell removal generates pulling forces necessary for tissue rearrangement. Efferocytosis by epithelial cells was observed during CND elimination. In this process, epithelial cells programmed to die are engulfed and subsequently phagocytosed by neighboring cells. This entire process involves a stationary distribution within the five different stages of phagocytosis and an apoptotic gradient along the CND. In this study, we used mathematical modeling approaches to analyze the spatiotemporal dynamics of this system and quantified not only the dwell time in each stage but also the flux of cells along the CND. We developed a Markov model of cellular engulfment and efferocytosis and coupled it to the transport equation to quantify dwell times and the flux of cells. The model was then solved and analyzed analytically. It revealed that cell death and processing increase along the CND towards the bladder. Model outcomes also matched biological observations and allowed us to quantify the temporal changes in the number of cells in each apoptotic stage. This apoptotic cell clearance machinery described in the model is probably the first example known so far in which its role was found to be absolutely necessary for tissue morphogenesis during normal development. This work thus provides important insights into spatiotemporal dynamics of cellular rearrangement in the CND.