Bridging protein electrostatics and cell behaviors

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Our research group determines in molecular detail how intracellular pH (pHi) dynamics regulates cell behaviors, with a focus on epithelial plasticity. Although pHi was previously thought to be relatively constant as a homeostatic mechanism, we now know that pHi changes during normal cell cycle progression, cell migration, and cell differentiation. Moreover, pHi is dysregulated in diseases, including being constitutively increased in cancers and decreased in neurodegenerative disorders. By bridging protein structure and electrostatics with cell biology we are revealing how pHi dynamics regulates cell behaviors through protonation of titrating amino acids as a post-translational modification to regulate protein structure and function. I will discuss our work on the design principles and functions of “pH sensors” described as endogenous proteins regulated within the cellular pH range, which have critical roles in cell division, migration, tumorigenesis and stem cell differentiation. I will present three approaches we have used to identify pH sensors. First is being informed by cell biology, highlighting our findings on pHi-regulated dysplasia and pH sensing by β-catenin, a component in cell adhesion and Wnt pathway activity. Second is being intrigued by distinct protein features predicted to be regulated by electrostatics, highlighted by our current work on FOX family transcription factors that have an invariant histidine with hydrogen bonding to nucleic acids in DNA promoters. Third is recognition of disease-associated charge-changing mutations, highlighted by our findings on arginine-histidine mutations in tumor suppressors and oncogenes that confer a gain in pH sensing. Collectively, these approaches are revealing new insights on the role of protein electrostatics in cell behaviors regulated by pHi dynamics.