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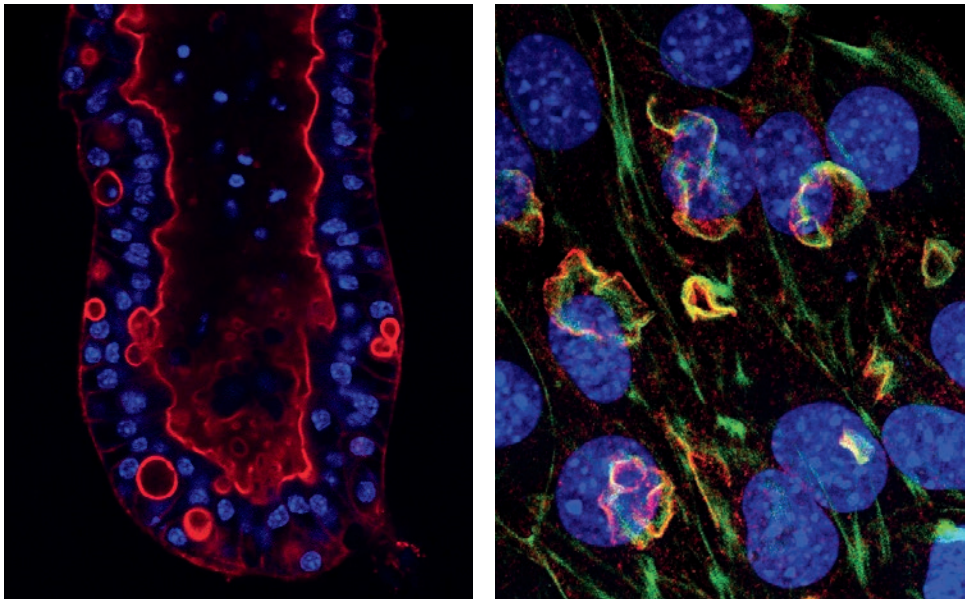
The McClatchey laboratory focuses on understanding how cells organize their outer surface – an important cellular compartment created by the interface between the cell membrane and underlying cortical cytoskeleton. This compartment governs the shape, identity and behavior of individual cells, as well as how they interact biochemically and mechanically with the extracellular environment. Normal cells modulate the features of the membrane:cytoskeleton interface to carry out key developmental processes and build functioning tissues. On the other hand, cancer cells exploit this compartment to interact inappropriately with other cells and with their environment during tumor initiation, invasion and metastasis. Our research stems from a longstanding quest to understand the molecular basis of a familial cancer syndrome caused by mutation of the *neurofibromatosis type 2 (NF2)* tumor suppressor gene. The *NF2*-encoded protein, Merlin, and closely related ERM proteins (Ezrin, Radixin and Moesin) are central architects of the cell cortex that have important roles in development and in many human cancers.

Understanding morphogenesis and tumorigenesis

The vast array of forms and functions exhibited by different cell types is enabled by the organization of specialized domains within the cell cortex such as the neuronal growth cone, immunological synapse and microvillus-studded apical surfaces of epithelial cells. Indeed, epithelial cells work together to establish discrete basal, lateral and apical surfaces as they organize into three dimensional structures that carry out organ-specific functions, such as the tubular networks of the lung, kidney, breast and liver. The spatial organization of cortical domains provides an essential layer of regulation to both biochemical and adhesive receptors on the cell surface, thereby limiting both proliferation and migration of cells in mature tissues. Alterations in the exquisite organization of epithelial structures are the earliest evidence of a developing tumor and signatures of tumor invasion and metastasis. The assembly of cortical domains requires the coordination of processes occurring at the plasma membrane and underlying cytoskeleton, and in particular, the formation of protein complexes that position membrane receptors, control their abundance and activity, and link them to the cortical cytoskeleton, which they modulate. The overarching goal of my laboratory is to understand how the dynamic organization of this cellular compartment contributes to morphogenesis and tumorigenesis. We have focused particular attention on the neurofibromatosis type 2 (NF2) tumor suppressor and closely related ERM proteins (Ezrin, Radixin and Moesin) - membrane:cytoskeleton linking proteins that simultaneously influence membrane complexes and the cortical actomyosin cytoskeleton, with the goals of delineating the molecular function of Merlin, identifying therapeutic targets for familial and sporadic *NF2*-mutant tumors and broadly examining the roles of Merlin/ERMs in development and cancer.



Left: Biliary cells form tubes with an actin- and ERM-rich (red) apical surface; Image credit: Evan O'Loughlin, PhD Student. Right: EGF stimulation rapidly triggers actin/ERM- (green) and pAkt (red) rich macropinocytic cups on the surface of Nf2-/- cells (the nucleus is stained blue in both images). Image credit: Christine Chiasson-MacKenzie, PhD.

Using mouse and bioengineered tissue culture models, we have identified important functions for Merlin and the ERM proteins in morphogenesis and tumorigenesis in many tissues. Cellular and molecular studies reveal that these phenotypes are driven by key, interdependent roles for Merlin and the ERM proteins in governing the dynamic and mechanical properties of the cortical cytoskeleton and, in particular, the inter-relationship between receptor tyrosine kinases (RTKs) and cortical cytoskeleton. Ongoing projects focus on the function of Merlin/ERMs and the membrane:cytoskeleton interface in establishing normal tissue architecture and contributing to tumor initiation and progression in biliary and mammary epithelial tubes, and in Schwann cell:axon relationships; complementary studies focus on how dynamic membrane:cytoskeleton remodeling of the cell surface triggers macropinocytosis, a form of bulk endocytosis that is exploited by some tumors for nutrient scavenging and a preferred conduit for the entry of many therapeutics into tumor cells. Thus far, our studies have provided novel insight into how the organization of the cell cortex governs the individual and collective behavior of cells and drives morphogenetic processes, how defective cortical organization contributes to tumor initiation and progression, and yielded unexpected therapeutic targets and avenues of translation for cancer therapy.

It is increasingly clear that cancer fundamentally reflects the aberrant re-enactment of developmental processes. We believe that the continued partnering of discovery-based science and translational studies will lead to novel therapeutic avenues while continuing to advance our understanding of the basic cellular activities that contribute to many human cancers.

Selected Publications:

Chiasson-MacKenzie C, Morris ZS, Liu CH, Bradford WB, Koorman T, **McClatchey AI**. Merlin/ERM proteins regulate growth factor-induced macropinocytosis and receptor recycling by organizing the plasma membrane:cytoskeleton interface. *Genes Dev.* 32(17-18): 1201-14, 2018 Sep 1.

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Chiasson-MacKenzie C, Morris ZS, Baca Q, Morris BA, Coker JK, Mirchev R, Jensen AE, Carey T, Stott S, Golan DE, **McClatchey AI**. NF2/Merlin mediates contact-dependent inhibition of EGFR mobility and internalization via cortical actomyosin. *J Cell Biol*. 211(2):391-405, 2015 Oct 26.

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Benhamouche S, Curto M, Saotome I, Gladden AB, Liu CH, Giovannini M, **McClatchey AI**. Nf2/Merlin controls progenitor homeostasis and tumorigenesis in the liver. *Genes Dev*. 24(16):1718-30, 2010 Aug 15.

*Denotes equal contribution