Leptomeningeal metastasis (LM) is an increasingly common, fatal complication of breast and lung cancer. Despite aggressive treatment, neurologic deficits accumulate rapidly, and patients generally succumb to LM within months. We must expand our limited mechanistic knowledge of this disease. Under homeostatic conditions, choroid plexus (ChP), highly vascularized structures within the brain ventricles, restrict the entry of macro-molecules and cells into the leptomeninges; however, select cancer cells can cross this barrier and grow within the leptomeningeal space. We hypothesize that interactions between cancer and ChP niche cells alter both the niche and the cancer cells, ultimately supporting LM. During neurogenesis, the ChP display substantial extracellular matrix (ECM) remodeling, which is elegantly modulated by dynamic spatiotemporal regulation of MMPs, Wnt signaling, among other effector proteins. Similarly, 2-photon imaging of ChP collected from mice harboring LM revealed a profound ECM remodeling of the ChP when compared with naive mice. This remodeling was accompanied by increased levels of MMP2 and MMP9 in the CSF. Furthermore, single-cell-RNA-sequencing of ChP reveals that Wnt is the top differentially expressed pathway in metastatic ChP in comparison with normal ChP, supporting a role for developmental signaling within the ChP in LM. Interestingly, SPARC, a major ECM modulator in tissue repair and an essential component of the stem cell niche chemoattractant factors secreted by the subventricular zone (SVZ), is enriched in metastatic mouse ChP suggesting that SVZ- and ChP-secreted signals are key in LM progression. The use of clinically-annotated human samples and mouse models of LM, and the integration of transcriptomics and proteomics enabled us to identify key signaling pathways, and capture the re-programming of ChP niche and cancer cells that unlock the leptomeningeal space to cancer cells. The
timeframe for this evolution will be further revealed by analysis of mouse and human samples at different stages of cancer progression.