Abstract

Melanoma brain metastasis (MBM) is linked to poor prognosis and low overall survival. We hypothesized that melanoma circulating tumor cells (CTCs) possess a gene signature significantly expressed and associated with MBM. Employing a multi-pronged approach, we provide first-time evidence identifying a common CTC gene signature for ribosomal protein large/small subunits (RPL/RPS) which associate with MBM onset and progression. Experimental strategies involved capturing, transcriptional profiling and interrogating CTCs, either directly isolated from blood of melanoma patients at distinct stages of MBM progression or from CTC-driven MBM in experimental animals. Second, we developed the first Magnetic Resonance Imaging (MRI) CTC-derived MBM xenograft model (MRI-MBM CDX) to discriminate MBM spatial and temporal growth, recreating MBM clinical presentation and progression. Third, we performed the comprehensive transcriptional profiling of MRI-MBM CDXs, along with longitudinal monitoring of CTCs from CDXs possessing/not possessing MBM. Our findings suggest that enhanced ribosomal protein content/ribogenesis may contribute to MBM onset. Since ribosome modifications drive tumor progression and metastatic development by remodeling CTC translational events, overexpression of the CTC RPL/RPS gene signature could be implicated in MBM development. Collectively, this study provides important insights for relevance of the CTC RPL/RPS gene signature in MBM, and identify potential targets for therapeutic intervention to improve patient care for melanoma patients diagnosed with or at high-risk of developing MBM.