Microglia are myeloid cells residing in the central nervous system that participate in inflammatory responses, promote injury and tissue repair. Clinical and experimental data show accumulation and tumor-driven functional polarization of microglia in glioma microenvironment that contributes to glioma pathogenesis. Using primary cultures of rat microglial cells and combining several techniques we characterized intracellular signaling pathways, global transcriptional responses and functions of these cells such as directional migration or phagocytosis. Data show that in contrast to a well-known inflammatory activation, tumor-educated microglia exhibit a unique, immunosuppressive, pro-invasive phenotype. Several inflammation-related signaling pathways and mediators were not activated in glioma-exposed microglia, while pathways implicated in structural reorganization and cell movement were activated. Specific genes coding for inhibitors of differentiation (Id1, Id3) and positive regulators of transcription (c-Myc) and many factors crucial for trafficking and differentiation of immune cells were up-regulated in microglia in course of acquisition of the pro-invasive phenotype. Our pioneering studies give novel insights into glioma-induced reprogramming of microglia. This newly discovered phenotype of glioma-educated microglia carries some features of the cytoprotective, immunosuppressive phenotype reported in certain immune subpopulations in neurological diseases. Our findings define molecular interactions, which are likely not limited to glioma microenvironment and have important clinical relevance.