Astrocyte-derived exosomal miR-19a reversibly downregulates PTEN expression in cancer cells to promote brain metastasis outgrowth

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Metastasis is the number one cause of cancer-related mortality. Development of life-threatening cancer metastases at distant organs requires disseminated tumor cells' adaptation to and co-evolution with the drastically different microenvironments of metastatic organ sites. Genetic profiling of metastases derived from different organ sites revealed that cancer cells of common origin manifest distinct gene expression patterns after metastasizing to different organs. The remarkable plasticity of metastatic tumor cells in response to different organ microenvironments underpins that the dynamic interplay between metastatic tumor cells and extrinsic signals at individual metastatic organ sites critically impacts the subsequent metastatic outgrowth. Yet, it is unclear when and how disseminated tumor cells acquire the essential traits from the microenvironment of metastatic organs that prime their subsequent outgrowth. In this study, we unexpectedly found that primary tumor cells with normal expression of PTEN, an important tumor suppressor, lose PTEN expression after dissemination to the brain, but not to other organs. PTEN level in PTEN-loss brain metastatic tumor cells is restored after leaving brain microenvironment. This brain microenvironment-dependent, reversible PTEN mRNA and protein down-regulation is epigenetically regulated by microRNAs (miRs) from astrocytes. Mechanistically, astrocyte-derived exosomes mediate an intercellular transfer of PTEN-targeting miRs, e.g., miR-19a, to metastatic tumor cells to inhibit PTEN expression. PTEN loss is rescued by astrocyte-specific depletion of PTEN-targeting miRs or by blockade of astrocyte exosome secretion *in vivo*, which also effectively suppresses brain metastasis *in vivo.* Furthermore, this adaptive PTEN loss in brain metastatic tumor cells reprograms tumor cells' secretome and leads to an increased secretion of cytokine chemokine (C-C motif) ligand 2 (CCL2) via activation of AKT and NF-kB. Tumor secreted CCL2 recruits Iba1+/CCR2+ myeloid cells that reciprocally enhance outgrowth of brain metastatic tumor cells via enhanced proliferation and reduced apoptosis. Our findings demonstrate a remarkable plasticity of PTEN expression in metastatic tumor cells in response to different organ microenvironments, highlighting an essential role of co-evolution between the metastatic cells and their microenvironment during the adaptive metastatic outgrowth. Our findings signify the dynamic and reciprocal cross-talk between tumor cells and the metastatic niche; importantly, they provide new opportunities for effective anti-metastasis therapies, especially of consequence for those brain metastasis patients who are in dire need.

Note: For more details, please see L. Zhang, et al, Nature, 527:100-4, 11/2015