CHARLOTTE FLUEH

Immunogenicity and tumor dormancy in brain metastases: comparison of central and peripheral markers of tumor dormancy in relation to NKG2DL expression

Objectives: Brain metastases are the most common intracranial tumors in adults and appear in about 25% percent of peripheral malignancies. Dormant tumor cells resemble a population of non-apoptotic, low proliferating tumor cells, which have the ability to be reactivated and are considered to be the source of recurrence. The Natural Killer Group 2, member D (NKG2D) receptor-ligand system is a major source of immunological escape. Cell-bound NKG2D-ligands (NKG2DL) such as MHC class I related molecule A and B (MICA and MICB), and the UL-16 binding protein family (ULBP1-6) are recognized by the NKG2D-receptor (NKG2D) and trigger cytotoxic effector activity in NK- and T-cells. To date, the immunological characteristics of dormant tumor cells are mostly unknown. We therefore aimed at investigating the characteristics of dormant tumor cells concerning their NKG2DL expression in cerebral metastases of breast and pulmonary cancer patients. Methods: We analyzed the expression profile and localization of NKG2DL (MICA, MICB, ULBP1, ULBP2) and several central (c; ephrin A5 [EphA5], insulin-like growth factor binding protein 5 [IGFBP5] and histone H2B type 1-K [H2BK]) and peripheral (p, platelet-derived growth factor beta [PDGFB], fibroblast growth factor 2 [FGF2] and hypoxia-inducible factor 1 alpha [HI-F1alpha]) dormancy markers in solid human brain metastases of breast and pulmonary cancer patients using two color immuno-staining (IS) and quantitative RT-PCR. Results: All investigated dormancy markers were detected in the investigated patients on mRNA and protein level. IS revealed a broad costaining of MICA and MICB with most peripheral dormancy markers in BC and with most peripheral and central dormancy markers in PC. ULBP1 and 2 showed costaining with most central dormancy markers in BC and PC. MICA and MICB were costained with each other, and ULBP1 with ULBP2. Central dormancy markers showed a broad costaining with each other and a partial costaining with peripheral dormancy markers. This effect was more pronounced in PC. Expression of central dormancy markers were negatively correlated with expression of NKG-2DL and vice versa. Conclusion: There are slight differences between the different tumor entities, but overall brain metastases seem to resemble a more peripheral type of dormancy rather than a central type. Due to their solid (co)-expression in the investigated samples, NKG2DL might play an important role in survival of dormant cells in cerebral metastases.