Tumor Associated Macrophages in SHH Subgroup of Medulloblastomas.

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Abstract

Purpose: Medulloblastoma in children can be categorized into at least four molecular subgroups, offering the potential for targeted therapeutic approaches to reduce treatment related morbidities. Little is known about the role of tumor microenvironment in medulloblastoma or its contribution to these molecular subgroups. Tumor microenvironment has been shown to be an important source for therapeutic targets in both adult and pediatric neoplasms. In this study, we investigated the hypothesis that expression of genes related to tumor-associated macrophages (TAMs) correlates with the medulloblastoma molecular subgroups and contributes to a diagnostic signature. Methods: Gene expression profiling using Human Exon Array (n=168) was analyzed to identify medulloblastoma molecular subgroups and expression of inflammation-related genes. Expression of 45 tumor-related and inflammation-related genes was analyzed in 83 medulloblastoma samples to build a gene signature predictive of molecular subgroups. TAMs in medulloblastomas (n=54) comprising the four molecular subgroups were assessed by immunohistochemistry (IHC). Results: A 31-gene medulloblastoma subgroup classification score inclusive of TAM-related genes (CD163, CSF1R) was developed with a misclassification rate of 2%. Tumors in the Sonic Hedgehog (SHH) subgroup had increased expression of inflammation-related genes and significantly higher infiltration of TAMs than tumors in the Group 3 or Group 4 subgroups (p<0.0001 and p<0.0001, respectively). IHC data revealed a strong association between location of TAMs and proliferating tumor cells. Conclusions: These data show that SHH tumors have a unique tumor microenvironment among medulloblastoma subgroups. The interactions of TAMs and SHH medulloblastoma cells may contribute to tumor growth revealing TAMs as a potential therapeutic target.

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