C3 / Padres Pedal the Cause 2018

"Targeting CD114 Signaling in Pediatric Medulloblastoma"

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SCIENTIFIC ABSTRACT

Children with high-risk medulloblastoma (MB) have poor survival rates despite intensive therapy and significant supportive care to minimize toxicity, including routine use of Granulocyte-Colony Stimulating Factor (G-CSF) to limit chemotherapy-induced neutropenia. Therapies directed against pathways important for MB cell survival and treatment resistance are likely to improve patient outcomes and reduce the frequency and severity of long-term side effects. We have recently identified a subset of MB cells that express CD114, the Granulocyte-Colony Stimulating Factor (G-CSF) receptor, and these cells demonstrate both increased growth after G-CSF treatment and resistance to chemotherapy compared to CD114-negative cells. These CD114-positive cells represent a population of chemoresistant MB cells that may contribute to poor outcomes in children with MB and whose survival could be promoted by the routine use of G-CSF in these children. However, the roles of CD114 expression and downstream signaling in MB pathogenesis are poorly understood, and the efficacy of targeting CD114-mediated signaling is unknown. The goals of this proposal are to determine the significance of CD114 expression in MB tumors and to determine whether targeting CD114 represents a novel therapeutic strategy in MB. The results of these studies will increase our understanding of the role of CD114 expression and function in MB pathogenesis and will potentially identify new therapeutic agents and novel targets for MB treatment.

LAY ABSTRACT

Children with high-risk, aggressive forms of medulloblastoma (MB) have poor chances of survival despite intensive chemotherapy and significant supportive care, including Granulocyte-Colony Stimulating Factor (GCSF). New treatments that kill MB cells resistant to chemotherapy are likely to reduce the chances of relapse and improve patient outcomes. We have recently found a small number of MB cells that have the Granulocyte-Colony Stimulating Factor (G-CSF) receptor (also called CD114) on their surface. We have shown that these CD114-positive cells grow faster after G-CSF treatment and are more resistant to chemotherapy compared to CD114-negative cells. These CD114-positive cells may contribute to the poor outcomes in children with highrisk MB, and their survival could be promoted by the routine use of G-CSF in children with MB after chemotherapy. However, the function of CD114 in MB tumors is not known. The goals of this proposal are to determine the function of CD114 in MB tumors and to determine whether CD114 could be a target for new types of MB treatment. We propose experiments determine which MB cells express CD114 in MB tumors and how CD114 expression contributes to the growth and survival of CD114-positive MB cells. The results of these studies will increase our understanding of the role of CD114 expression and function in MB tumors and will potentially identify new treatments for children with MB.