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Immune checkpoint inhibition in hypermutant glioblastoma multiforme

Pediatric glioblastoma multiforme has a very poor prognosis, with a median survival of less than six months. Many childhood glioblastoma multiformes (GBMs) are associated with cancer predisposition syndromes, including biallelic mismatch repair deficiency syndrome (bMMRD). In this syndrome, there are homozygous mutations in one of the four mismatch repair genes—*PMS2, MLH1, MSH2*, and *MSH6*—which cause affected patients to develop malignancies, usually within the first two decades of life. Due to the lack of proofreading during DNA replication, the GBMs in these patients have the highest somatic mutation load among human cancers. Treatment strategies that include immune checkpoint inhibition, either by targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed death-1/programmed death-ligand 1 (PD-1/PD-L1), have a higher efficacy in tumors that have a high somatic mutation load. Therefore, in a recent study by Bouffet, et al., the authors hypothesized that immune checkpoint inhibition may be effective in bMMRD-associated tumors, including bMMRD-associated pediatric GBM. They performed whole exome sequencing on bMMRD-associated cancers, including 21 GBMs, and demonstrated that bMMRD-associated brain tumors had the highest rates of mutations, likely because of secondary mutations in DNA polymerase. Because neoantigen load correlates with response to immunotherapy, and not necessarily mutational status, the authors assessed the neoantigen load of bMMRD-associated tumors. They examined each somatic variant to determine if a novel peptide antigen would be created and how well these potential antigens would bind to the major histocompatibility complex I (MHC-I). They found that bMMRD-associated GBMs had a remarkably higher number of predicted neoantigens—approximately seven to 16 times higher than that seen in immunoresponsive melanomas, lung cancers, and microsatellite-unstable gastrointestinal cancers. Based on these findings, the authors treated two siblings—a six-year-old girl and a 3.5-year-old boy, both of whom had bMMRD-associated GBMs that had recurred after surgical and radiation therapy—with the immune checkpoint inhibitor nivolumab. Molecular investigation had confirmed the diagnosis of bMMRD, as both patients had homozygous c.2117delA mutations in *PMS2* and loss of PMS2 immunohistochemical staining in tumor and background tissue. In most cases, despite standard-of-care salvage therapy, recurrent pediatric GBMs will progress within one to two months, and survival is only three to six months after recurrence. After the siblings in this therapeutic trial of nivolumab were initially infused, they developed seizures due to edema in areas of tumor dissemination. The seizures were treated with steroids, anti-seizure medication, and supportive care, and both patients had significant tumor shrinkage by the end of therapy, as demonstrated on magnetic resonance imaging. After nine and five months of therapy, respectively, the girl and boy resumed normal schooling and normal daily activities. Overall, this study provides additional evidence that immune checkpoint inhibition therapy may be most effective in tumors with high numbers of somatic mutations and neoantigens. Therefore, immune checkpoint inhibition may be a viable treatment strategy for tumors associated with primary germline or secondary somatic mismatch repair deficiency.

Bouffet E, Larouche V, Campbell BB, et al. Immune checkpoint inhibition for hypermutant glioblastoma multiforme resulting from germline biallelic mismatch repair deficiency [published online ahead of print March 21, 2016]. *J Clin*

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Link between inactivating variants of ANGPTL4 and coronary artery disease risk

Elevated levels of serum triglycerides are associated with increased risk of cardiovascular disease, and some recent studies have even established a causative link. The enzyme lipoprotein lipase (LPL) hydrolyzes triglycerides to release fatty acids for use in tissues. Mutational studies have demonstrated that alterations that increase LPL activity reduce triglyceride levels and decrease cardiovascular disease risk, whereas alterations that decrease LPL activity have the opposite effect. Among the endogenous modulators that affect LPL activity is angiopoietin-like 4 (ANGPTL4), which has been demonstrated to inhibit LPL in vivo and in vitro. It has been shown that inactivating mutations in *ANGPTL4* increase LPL activity, thereby reducing serum triglyceride levels, but the effect on coronary artery disease is disputed. Two studies, simultaneously published in The *New England Journal of Medicine*, examined the effects of *ANGPTL4* mutations. In the first study, reported by Dewey, et al., the authors sequenced the exons of *ANGPTL4* in samples from 42,930 patients enrolled in the DiscovEHR human genetics study from 2007 through 2015. Of these patients, 1,661 were heterozygous and 17 were homozygous for an E40K germline variant that is an inactivating variant of *ANGPTL4*. An additional 75 patients had 13 other inactivating mutations in *ANGPTL4*. The patients with inactivating mutations in *ANGPTL4* had significantly lower levels of serum triglycerides and significantly higher levels of high-density lipoprotein (HDL), while the levels of low-density lipoprotein (LDL) and total cholesterol showed no significant difference. The patients with the E40K inactivating variant also had a significantly decreased risk of angiographically-defined coronary artery disease, with an odds ratio of 0.81. The authors then examined whether modulating *ANGPTL4* activity could be a viable treatment strategy in animal models. Administration of a monoclonal antibody to ANGPTL4 reduced serum triglyceride levels in mice that had a predisposition to hypertriglyceridemia, obese rhesus monkeys with dyslipidemia, and cynomolgus monkeys fed a high-fat diet. In many of the animals, however, granulomatous lipid accumulation was observed in mesenteric lymph nodes. Although the authors did not find any significant difference in the rates of mesenteric lymphadenopathy or other abdominal disorders in patients with inactivating *ANGPTL4* mutations, such a finding in the animal models raises concern about the viability of such a treatment strategy. In the second study, reported by Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia investigators, exome screening was performed in 72,868 patients with coronary artery disease and 120,770 control patients to identify low-frequency variants associated with coronary artery disease. Mutations in *ANGPTL4* were confirmed to be associated with decreased levels of triglycerides, higher levels of HDL, and protection against coronary artery disease. The study also identified other mutations associated with coronary artery disease. Overall, these two studies highlight the importance of lipid metabolism in the development of coronary artery disease, suggesting that enhancement of LPL pathway activity may be a possible therapeutic target in the future.

Dewey FE, Gusarova V, O'Duschlaine C, et al. Inactivating variants in *ANGPTL4* and risk of coronary artery disease. *N Engl J Med.* 2016;374(12):1123–1133.

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Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia investigators. Coding variation in *ANGPTL4, LPL,* and *SVEP1* and the risk of coronary disease. *N Engl J Med.* 2016;374(12):1134–1144.

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