Dong et al. found that cholesterol levels in GBM tissues are abnormally high, and glioma-supportive macrophages (GSMs), an essential “cholesterol factory”, demonstrated aberrantly hyperactive cholesterol metabolism and efflux, providing cholesterol to fuel GBM growth and induce CD8+ T cells exhaustion. Subsequent bioinformatics analysis confirmed that high 7-Dehydrocholesterol reductase (DHCR7) level in GBM tissues was concomitant with increased cholesterol biosynthesis, suppressed tumoricidal immune response, and poor patient survival and DHCR7 expression level was significantly elevated in GSMs. Therefore, they reported an intracavitary sprayable nanoregulator-encased hydrogel system to modulate the cholesterol metabolism of GSMs. The degradable nanoregulator-mediated ablation of DHCR7 in GSMs effectively suppressed cholesterol supply and activated T-cell immunity. Moreover, the combination of Toll-like receptor 7/8 (TLR7/8) agonists significantly promoted GSM polarization to antitumor phenotypes and ameliorated the immunosuppressive TME. Treatment with the hybrid system exhibited superior antitumor effects in the orthotopic GBM tumor model and postsurgical recurrence model. Altogether, the findings unravel the role of GSMs DHCR7/cholesterol signaling in the regulation of immunosuppressive TME, presenting a potential glioblastoma treatment strategy that warrants further clinical trials [1)].

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Dong Y, Zhang J, Wang Y, Zhang Y, Rappaport D, Yang Z, Han M, Liu Y, Fu Z, Zhao X, Tang C, Shi C, Zhang D, Li D, Ni S, Li A, Cui J, Li T, Sun P, Benny O, Zhang C, Zhao K, Chen C, Jiang X. Intracavitary Spraying of Nanoregulator-Encased Hydrogel Modulates Cholesterol Metabolism of Glioma-Supportive Macrophage for Postoperative Glioblastoma Immunotherapy. Adv Mater. 2023 Dec 21:e2311109. doi: 10.1002/adma.202311109. Epub ahead of print. PMID: 38127403.