Immunometabolism

The changes that occur in intracellular metabolic pathways in immune cells during activation. Broadly, immunometabolic research records the physiological functioning of the immune system in the context of different metabolic conditions in health and disease. These studies can cover molecular and cellular aspects of immune system function in vitro, in situ, and in vivo, under different metabolic conditions. For example, highly proliferative cells such as cancer cells and activating T cells undergo metabolic reprogramming, increasing glucose uptake to shift towards aerobic glycolysis during normoxia. While aerobic glycolysis is an inefficient pathway for ATP production in quiescent cells, this so-called “Warburg effect” supports the bioenergetic and biosynthetic needs of rapidly proliferating cells.

Immunotherapy has yielded significant improvements in survival for many cancer types, but its impact on glioblastoma (GBM) has been relatively muted. There is a growing interest in understanding the role of cancer metabolism and its role in tumor growth and therapeutic response. Thus, it is equally important to consider the clinical implications of immune cell metabolism on cancer progression and implications for therapeutic development. Our objective is to present new developments in immunometabolic research that are relevant to immunotherapy development for high-grade gliomas.

Methods: A literature search and review was conducted, regarding original research articles studying metabolic pathways of immune cells in high-grade gliomas. Searches were conducted in PubMed and Embase databases on May 15 and June 13, 2022. English-language original research articles were selected and prioritized based on their inclusion of findings related to metabolic changes in myeloid and lymphoid cells in the glioma tumor microenvironment.

Key content and findings: There are many metabolic mechanisms by which immune cells in high-grade gliomas, like GBM, contribute to tumor growth and persistence via immunosuppression and high therapeutic resistance. There are also several ways that metabolic optimization has already been shown to improve immunotherapies already in clinical trials or in use, including dendritic cell vaccines and chimeric antigen receptor T cells.

Conclusions: The implications of immunometabolic research presented here should be taken into consideration in future research and immunotherapy development of high-grade gliomas for our best chances at improving patient survival. [1)].

2: Rodríguez-Morales J, Guartazaca-Guerrero S, Rizo-Téllez SA, Viurcos-Sanabria R, Barrón EV, Hernández-Valencia AF, Nava P, Escobedo G, Carrillo-Ruiz JD, Méndez-García LA. Blood-brain Barrier Damage is Pivotal for SARS-CoV-2 Infection to the Central Nervous System. Exp Neurobiol. 2022 Aug 31;31(4):270-276. doi: 10.5607/en21049. PMID: 36050226.

3: Viurcos-Sanabria R, Manjarrez-Reyna AN, Solleiro-Villavicencio H, Rizo-Téllez SA, Méndez-García LA, Viurcos-Sanabria V, González-Sanabria J, Arroyo-Valerio A, Carrillo-Ruíz JD, González-Chávez A, León-Pedroza JI, Flores-Mejía R, Rodríguez- Cortés O, Escobedo G. In Vitro Exposure of Primary Human T Cells and Monocytes to Polyclonal Stimuli Reveals a Basal Susceptibility to Display an Impaired Cellular Immune Response and Develop Severe COVID-19. Front Immunol. 2022 Jul 1;13:897995. doi: 10.3389/fimmu.2022.897995. PMID: 35860236; PMCID: PMC9289744.

4: Bueno-Hernández N, Carrillo-Ruíz JD, Méndez-García LA, Rizo-Téllez SA, Viurcos-Sanabria R, Santoyo-Chávez A, Márquez-Franco R, Aguado-García A, Baltazar-López N, Tomita-Cruz Y, Barrón EV, Sánchez AL, Márquez E, Fossion R, Rivera AL, Ruelas L, Lecona OA, Martínez-Mekler G, Müller M, Arroyo-Valerio AG, Escobedo G. High Incidence Rate of SARS-CoV-2 Infection in Health Care Workers at a Dedicated COVID-19 Hospital: Experiences of the Pandemic from a Large Mexican Hospital. Healthcare (Basel). 2022 May 12;10(5):896. doi: 10.3390/healthcare10050896. PMID: 35628032; PMCID: PMC9141357.

5: Bernstock JD, Kang KD, Klinger NV, Olsen HE, Gary S, Totsch SK, Ghajar-Rahimi G, Segar D, Thompson EM, Darley-Usmar V, Mott BT, Peruzzotti-Jametti L, Friedman GK. Targeting oncometabolism to maximize immunotherapy in malignant brain tumors. Oncogene. 2022 May;41(19):2663-2671. doi: 10.1038/s41388-022-02312-y. Epub 2022 Apr 16. PMID: 35430605; PMCID: PMC9081266.

6: Patel T, Carnwath TP, Wang X, Allen M, Lincoln SJ, Lewis-Tuffin LJ, Quicksall ZS, Lin S, Tutor-New FQ, Ho CCG, Min Y, Malphrus KG, Nguyen TT, Martin E, Garcia CA, Alkharboosh RM, Grewal S, Chaichana K, Wharen R, Guerrero-Cazares H, Quinones-Hinojosa A, Ertekin-Taner N. Transcriptional landscape of human microglia implicates age, sex, and APOE-related immunometabolic pathway perturbations. Aging Cell. 2022 May;21(5):e13606. doi: 10.1111/acel.13606. Epub 2022 Apr 6. PMID: 35388616; PMCID: PMC9124307.

7: Mendoza-Martínez VM, Zavala-Solares MR, Espinosa-Flores AJ, León-Barrera KL, Alcántara-Suárez R, Carrillo-Ruíz JD, Escobedo G, Roldan-Valadez E, Esquivel- Velázquez M, Meléndez-Mier G, Bueno-Hernández N. Is a Non-Caloric Sweetener-Free Diet Good to Treat Functional Gastrointestinal Disorder Symptoms? A Randomized Controlled Trial. Nutrients. 2022 Mar 5;14(5):1095. doi: 10.3390/nu14051095. PMID: 35268070; PMCID: PMC8912523.

8: Brydges CR, Bhattacharyya S, Dehkordi SM, Milaneschi Y, Penninx B, Jansen R, Kristal BS, Han X, Arnold M, Kastenmüller G, Bekhbat M, Mayberg HS, Craighead WE, Rush AJ, Fiehn O, Dunlop BW, Kaddurah-Daouk R; Mood Disorders Precision Medicine Consortium. Metabolomic and inflammatory signatures of symptom dimensions in major depression. Brain Behav Immun. 2022 May;102:42-52. doi: 10.1016/j.bbi.2022.02.003. Epub 2022 Feb 4. PMID: 35131442; PMCID: PMC9241382.

9: Rizo-Téllez SA, Méndez-García LA, Rivera-Rugeles AC, Miranda-García M, Manjarrez-Reyna AN, Viurcos-Sanabria R, Solleiro-Villavicencio H, Becerril- Villanueva E, Carrillo-Ruíz JD, Cota-Arce JM, Álvarez-Lee A, De León-Nava MA, Escobedo G. The Combined Use of Cytokine Serum Values with Laboratory Parameters Improves Mortality Prediction of COVID-19 Patients: The Interleukin-15-to-Albumin Ratio. Microorganisms. 2021 Oct 16;9(10):2159. doi: 10.3390/microorganisms9102159. PMID: 34683480; PMCID: PMC8539806.

10: Chaudhry SR, Stadlbauer A, Buchfelder M, Kinfe TM. Melatonin Moderates the Triangle of Chronic Pain, Sleep Architecture and Immunometabolic Traffic. Biomedicines. 2021 Aug 9;9(8):984. doi: 10.3390/biomedicines9080984. PMID: 34440187; PMCID: PMC8392406.

11: Korshoj LE, Shi W, Duan B, Kielian T. The Prospect of Nanoparticle Systems for Modulating Immune Cell Polarization During Central Nervous System Infection. Front Immunol. 2021 Jun 23;12:670931. doi: 10.3389/fimmu.2021.670931. PMID: 34248952; PMCID: PMC8260670.

12: Guartazaca-Guerrero S, Rodríguez-Morales J, Rizo-Téllez SA, Solleiro- Villavicencio H, Hernández-Valencia AF, Carrillo-Ruiz JD, Escobedo G, Méndez- García LA. High Levels of IL-8 and MCP-1 in Cerebrospinal Fluid of COVID-19 Patients with Cerebrovascular Disease. Exp Neurobiol. 2021 Jun 30;30(3):256-261. doi: 10.5607/en21009. PMID: 34230225; PMCID: PMC8278137.

13: Mohan AA, Tomaszewski WH, Haskell-Mendoza AP, Hotchkiss KM, Singh K, Reedy JL, Fecci PE, Sampson JH, Khasraw M. Targeting Immunometabolism in Glioblastoma. Front Oncol. 2021 Jun 16;11:696402. doi: 10.3389/fonc.2021.696402. PMID: 34222022; PMCID: PMC8242259.

14: Tye SJ, Borreggine K, Price JB, Sutor SL, Cuéllar-Barboza AB, McElroy SL, Biernacka JM, Frye MA. Dynamic insulin-stimulated mTOR/GSK3 signaling in peripheral immune cells: Preliminary evidence for an association with lithium response in bipolar disorder. Bipolar Disord. 2022 Feb;24(1):39-47. doi: 10.1111/bdi.13081. Epub 2021 May 13. PMID: 33864716.

15: Fleeman RM, Proctor EA. Astrocytic Propagation of Tau in the Context of Alzheimer's Disease. Front Cell Neurosci. 2021 Mar 17;15:645233. doi: 10.3389/fncel.2021.645233. PMID: 33815065; PMCID: PMC8010320.

16: Shu L, Liu Y, Li J, Wu X, Li Y, Huang H. Landscape Profiling Analysis of DPP4 in Malignancies: Therapeutic Implication for Tumor Patients With Coronavirus Disease 2019. Front Oncol. 2021 Feb 4;11:624899. doi: 10.3389/fonc.2021.624899. PMID: 33614513; PMCID: PMC7890191.

17: Baban B, Braun M, Khodadadi H, Ward A, Alverson K, Malik A, Nguyen K, Nazarian S, Hess DC, Forseen S, Post AF, Vale FL, Vender JR, Hoda MN, Akbari O, Vaibhav K, Dhandapani KM. AMPK induces regulatory innate lymphoid cells after traumatic brain injury. JCI Insight. 2021 Jan 11;6(1):e126766. doi: 10.1172/jci.insight.126766. PMID: 33427206; PMCID: PMC7821592.

18: Kinfe TM, Stadlbauer A, Bozhkov Y, Kremenevski N, Brandner S, Buchfelder M, Chaudhry SR. The Diagnostic and Therapeutic Role of Leptin and Its Receptor ObR in Glioblastoma Multiforme. Cancers (Basel). 2020 Dec 9;12(12):3691. doi: 10.3390/cancers12123691. PMID: 33316976; PMCID: PMC7764087.

19: Rizo-Téllez SA, Méndez-García LA, Flores-Rebollo C, Alba-Flores F, Alcántara-Suárez R, Manjarrez-Reyna AN, Baltazar-López N, Hernández-Guzmán VA, León-Pedroza JI, Zapata-Arenas R, González-Chávez A, Hernández-Ruíz J, Carrillo- Ruíz JD, Serrano-Loyola R, Guerrero-Avendaño GML, Escobedo G. The Neutrophil-to- Monocyte Ratio and Lymphocyte-to-Neutrophil Ratio at Admission Predict In-Hospital Mortality in Mexican Patients with Severe SARS-CoV-2 Infection (Covid-19). Microorganisms. 2020 Oct 10;8(10):1560. doi: 10.3390/microorganisms8101560. PMID: 33050487; PMCID: PMC7600553.

20: Zopfs D, Bousabarah K, Lennartz S, Santos DPD, Schlaak M, Theurich S, Reimer RP, Maintz D, Haneder S, Große Hokamp N. Evaluating body composition by combining quantitative spectral detector computed tomography and deep learning- based image segmentation. Eur J Radiol. 2020 Sep;130:109153. doi: 10.1016/j.ejrad.2020.109153. Epub 2020 Jul 12. PMID: 32717577.

21: Chao CC, Gutiérrez-Vázquez C, Rothhammer V, Mayo L, Wheeler MA, Tjon EC, Zandee SEJ, Blain M, de Lima KA, Takenaka MC, Avila-Pacheco J, Hewson P, Liu L, Sanmarco LM, Borucki DM, Lipof GZ, Trauger SA, Clish CB, Antel JP, Prat A, Quintana FJ. Metabolic Control of Astrocyte Pathogenic Activity via cPLA2-MAVS. Cell. 2019 Dec 12;179(7):1483-1498.e22. doi: 10.1016/j.cell.2019.11.016. Epub 2019 Dec 5. PMID: 31813625; PMCID: PMC6936326.

22: Kinfe TM, Buchfelder M, Chaudhry SR, Chakravarthy KV, Deer TR, Russo M, Georgius P, Hurlemann R, Rasheed M, Muhammad S, Yearwood TL. Leptin and Associated Mediators of Immunometabolic Signaling: Novel Molecular Outcome Measures for Neurostimulation to Treat Chronic Pain. Int J Mol Sci. 2019 Sep 24;20(19):4737. doi: 10.3390/ijms20194737. PMID: 31554241; PMCID: PMC6802360.

23: Al-Sharea A, Lee MKS, Whillas A, Michell DL, Shihata WA, Nicholls AJ, Cooney OD, Kraakman MJ, Veiga CB, Jefferis AM, Jackson K, Nagareddy PR, Lambert G, Wong CHY, Andrews KL, Head GA, Chin-

Dusting J, Murphy AJ. Chronic sympathetic driven hypertension promotes atherosclerosis by enhancing hematopoiesis. Haematologica. 2019 Mar;104(3):456-467. doi: 10.3324/haematol.2018.192898. Epub 2018 Oct 25. PMID: 30361420; PMCID: PMC6395347.

24: Vaibhav K, Braun M, Khan MB, Fatima S, Saad N, Shankar A, Khan ZT, Harris RBS, Yang Q, Huo Y, Arbab AS, Giri S, Alleyne CH Jr, Vender JR, Hess DC, Baban B, Hoda MN, Dhandapani KM. Remote ischemic post-conditioning promotes hematoma resolution via AMPK-dependent immune regulation. J Exp Med. 2018 Oct 1;215(10):2636-2654. doi: 10.1084/jem.20171905. Epub 2018 Sep 6. PMID: 30190288; PMCID: PMC6170180.

25: Agarwal P, Pajor MJ, Anson DM, Guda MR, Labak CM, Tsung AJ, Velpula KK. Elucidating immunometabolic targets in glioblastoma. Am J Cancer Res. 2017 Oct 1;7(10):1990-1995. PMID: 29119048; PMCID: PMC5665846.

1)

Wu JY, Ren AL, Lim M. Immunometabolism, a new therapeutic development for immunotherapies of high-grade gliomas: a narrative review. Chin Clin Oncol. 2022 Aug;11(4):26. doi: 10.21037/cco-22-58. PMID: 36098097.