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Molecular Physiology of G-CIMP+ Glioblastomas: Therapeutic Implications

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A fundamental premise of gene therapy as it pertains to oncology is precision medicine, whereby therapeutic intervention is matched to unique vulnerabilities dictated molecular physiology of the cancer [1]. Cancers previously thought to be single clinical entities are now stratified based on these molecular physiologies [2]. As an example, glioblastoma, the most common form of primary adult brain cancer [3], is now recognized as an umbrella term that encapsulates a spectrum of subtypes that are defined by shared molecular physiologies [4]. A notable glioblastoma subtype involves the Glioma CpG IslandMethylator (G-CIMP) phenotype.

The G-CIMP+ glioblastomas share in common hypermethylationin the CpG islands of a large number of genomic regions [5]. In turn, the aberrant methylationdown-regulates expression of selectgenes resulting in an unique physiologic state. Patients afflicted with G-CIMP+ glioblastoma tend to be younger and exhibit more favorable clinical course [5]. Until recently, the molecular physiology associated with this state remains poorly understood.

Our recent findings suggest that mitogenic engines of G-CIMP+ glioblastomas fundamentally differ from those G-CIMP- glioblastomas. Proliferation of G-CIMP- glioblastomas is driven by hyper-activation of Receptor Tyrosine Kinases (RTKs) [6]. RTK signaling is suppressed in G-CIMP+ glioblastomas. The expressions of genes required for RTK signaling are down-regulated via epigenetic mechanisms in G-CIMP- glioblastomas. Accordingly, these tumors are therapeutically resistant to targeted therapies directed against RTK signaling in pre-clinical models [6].

These findings harbor significant implications in terms of glioblastoma therapeutic development. Consideration should be given to stratify glioblastoma patients by G-CIMP status in clinical trials testing RTK-selective agents. Such stratification would enable one to determine the validity of the published pre-clinical findings that G-CIMP+ tumors are resistant to RTK inhibition [6]. Additionally, the results suggest potential clinical utility of therapeutic approaches targeting key epigenetic gene regulators or unique vulnerabilities associated with the G-CIMP+ epigenetic state. Ultimately, meaningful advances in glioblastoma therapy will require the recognition of G-CIMP+ glioblastoma as a distinct disease state and an understanding of the molecular physiology of that state.

References

1. Simon R, Roychowdhury S (2013) Implementing personalized cancer genomics in clinical trials. Nat Rev Drug Discov 12: 358-369.
2. Bartek J, Jr., Ng K, Bartek J, Fischer W, Carter B, et al. (2012) Key concepts in glioblastoma therapy. J Neurol Neurosurg Psychiatry 83: 753-760.
3. Ng K, Kim R, Kesari S, Carter B, Chen CC (2013) Genomic profiling of glioblastoma: convergence of fundamental biologic tenets and novel insights. J Neurooncol 107: 1-12.
4. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, et al. (2010) Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 17: 98-110.
5. Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, et al. (2010) Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell 17: 510-522.
6. Li J, Taich ZJ, Goyal A, Gonda D2, Akers J2, et al. (2014) Epigenetic suppression of EGFR signaling in G-CIMP+ glioblastomas. Oncotarget 5: 7342-7356.