Molecular Physiology of G-CIMP+ Glioblastomas: Therapeutic Implications

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 hypermethylation in the CpG islands of a large number of genomic regions [5]. In turn, the aberrant methylation down-regulates expression of select genes 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