Novel Cancer Drug Targets from Comparison of Patient-Matched Genomic Profiles
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Introduction
The Cancer Genome Atlas (TCGA) is a national effort to accelerate cure for cancer. This initiative chose to study Glioblastoma multiforme (GBM), a fast-growing and most common brain tumor in adults. Patients with GBM have a poor prognosis and usually survive less than 15 months following diagnosis. Currently there are no effective long-term treatments for this disease.

Mathematical Method: GSVD

The GSVD uncovers one global pattern of tumor-exclusive co-occurring copy-number alterations (CNAs) that is correlated, possibly coordinated, with GBM survival and response to chemotherapy (Fig. 2 a–c, Fig. 4).

• The pattern reveals novel CNAs including the cell cycle-regulated serine/threonine kinase encoding TLK2, the cyclin E1-encoding CCNE1 which has been linked with many cancers but not GBM, and the Rb-binding protein-encoding KDM5A which has been recently implicated in cancer drug tolerance.

• Amplification of TLK2, which encodes for a biochemically putative drug target, has been correlated with overexpression in several other cancers. The Kaplan-Meier median survival time with TLK2/METTL2A amplification is 5 months longer than that for the remaining patients, suggesting that drug-targeting the kinase that TLK2 encodes may affect not only the pathogenesis but also the prognosis of GBM.

GSVD Identifies and Removes Experimental Variations

The GSVD removes from the global pattern copy-number variations that occur in the normal human genome, e.g., female-specific X chromosome amplification (Fig. 2 d–f), and experimental variations, (Fig. 3) without a-priori knowledge of these variations.

Conclusion

The global pattern revealed by GSVD includes most known GBM-associated changes in chromosome numbers and focal CNAs and uncovers several previously unreported CNAs, including the biochemically putative drug target-encoding TLK2.

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References
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