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Targeting Softness within Tumor Hardness

So far, there is general assumption that accumulation of the tumorigenic genetic alteration leads to cancer and targeting such tumorigenic alteration lead to cure. Apparently, this assumption is correct but not complete. In a tumor there are usually numerous such genetic alteration and all of them are not associated with tumorigenicity. Targeting tumorigenic alteration for cure could be possible if all of such alteration are known and all of such alteration could be targeted. However, we do not know all such tumorigenic alteration and cannot target all of them. Even if we target some of the apparent alteration, the tumor may show transient suppression or cure but will be relapsed again probably via the remaining or untargeted tumorigenic alteration.

Along with tumorigenic alteration, a tumor could be accompanied by other genetic alteration or phenomenon, not necessarily tumorigenic, which could make a tumor more susceptible than other cell. Targeting such acquired vulnerable pathway may leads to easy, early and efficient elimination of tumor especially those with complicated or multiple tumorigenic alteration. In this study, the authors propose a new hypothesis and provide a master class proof that targeting acquired vulnerable pathway may cure glioblastoma tumor more efficiently and safely.

Introduction

Cell, Volume 157, Issue 2, 10 April 2014, Pages 313–328

Vulnerability of Glioblastoma Cells to Catastrophic Vacuolization and Death Induced by a Small Molecule. Kitambi et al.

Abstract

Glioblastoma multiforme (GBM) is the most aggressive form of brain cancer with marginal life expectancy. Based on the assumption that GBM cells gain functions not necessarily involved in the cancerous process, patient-derived glioblastoma cells (GCs) were screened to identify cellular processes amenable for development of targeted treatments. The quinine-derivative NSC13316 reliably and selectively compromised viability. Synthetic chemical expansion reveals delicate structure-activity relationship and analogs with increased potency, termed Vacquinols. Vacquinols stimulate death by membrane ruffling, cell rounding, massive macropinocytic vacuole accumulation, ATP depletion, and cytoplasmic membrane rupture of GCs. The MAP kinase MKK4, identified by a shRNA screen, represents a critical signaling node. Vacquinol-1 displays excellent in vivo pharmacokinetics and brain exposure, attenuates disease progression, and prolongs survival in a GBM animal model. These results identify a vulnerability to massive vacuolization that can be targeted by small molecules and point to the possible exploitation of this process in the design of anticancer therapies.