Abstract

Genotype-based cancer treatments, in which the signaling pathways that are altered by oncogenic mutations are targeted by highly selective molecules, hold great promise for cancer treatment as these targeted drugs often lead to dramatic clinical responses with reduced toxicity. However, not all cancer driver mutations are druggable. For example, loss-of-function alterations of tumor suppressors are not directly targetable. Mutations affecting various subunits of SWI/SNF chromatin remodeling/tumor suppressor complex, such as *SMARCA4* encoding one of the two mutually exclusive ATPases, are found in ~25% of all human cancers. *SMARCA2*, the paralog of *SMARCA4*, is rarely mutated but often epigenetically silenced in tumors. Concurrent loss of *SMARCA4/2* characterizes subsets of ovarian and lung cancers associated with very poor outcome. In addition to tumor suppressor loss, some activating oncogenic mutations such as those in *KRAS*, have proven to be very difficult to target. Although *RAS* inhibitor sotorasib has been recently approved to treat $KRAS^{G12C}$ lung cancer with less than 50% response rate, it is not effective against other *KRAS* mutations. Thus, alternative treatment options are needed for targeting these cancers that remain difficult to treat.

We have employed functional screening to unbiasedly identify the novel druggable susceptibility in these hard-to-treat cancers and uncovered that: 1) *SMARCA4/2*-deficient cancers are vulnerable to inhibition to oxidative phosphorylation (OXPHOS) and glutamine metabolism; 2) *KRAS*-mutant cancers acquire selective vulnerability to ferroptosis promoting agent, following co-targeting *BRD4* and *CDK4/6*. Specifically, *SMARCA4/2*-loss leads to downregulation of glucose transporter *GLUT1*, causing reduced glucose uptake and glycolysis accompanied with increased glutamine import by transporter *SLC38A2* to fuel OXPHOS. Consequently, *SMARCA4/2* deficient cells and tumors are highly sensitive to inhibitors targeting OXPHOS or glutamine metabolism. Supplementation of alanine, also imported by *SLC38A2* restricts glutamine uptake by competition and selectively induces cell death in these deficient cancer cells and tumors. In *KRAS*-mutant cancers, we found that co-targeting *BRD4* and *CDK4/6* is synergistic in inducing strong senescence in a reactive oxygen species (ROS)- and *RB*- dependent manner. Mechanistically, *BRD4*-inhibition enhanced cell cycle arrest and reactive oxygen species (ROS) accumulation both required for this senescence induction, which elevated *GPX4*, a peroxidase against ROS-triggered ferroptosis. Consequently, addition of a *GPX4* inhibitor selectively induced ferroptotic death in these senescent cells leading to tumor regression. Collectively, our findings uncover multiple druggable susceptibility in these hard-to-treat cancers, which may ultimately be helpful to patients.

McGill University

Graduate and Postdoctoral Studies

Final Oral Examination
for the Degree of
Doctor of Philosophy
of **Xianbing Zhu**

of the Department of Biochemistry**, on April 18, 2023 @ 9:00 am** Via Zoom.

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***Xianbing Zhu**, *Zheng Fu, *Shary Yuting Chen, Dionzie Ong, Giulio Aceto Rebecca Ho, Jutta Steinberger, Anie Monast, Virginie Pilon, Eunice Li, Monica Ta, Kyle Ching, Bianca Adams, Gian Luca Negri, Luc Choiniere, Lili Fu, Kitty Pavlakis, Patrick Pirrotte, Daina Zofija Avizonis, Jeffrey Trent, Bernard E. Weissman, Ramon Klein Geltink, Gregg B. Morin, Morag Park, David G. Huntsman, William D. Foulkes, Yemin Wang[§] and Sidong Huang[§]. Alanine supplementation exploits glutamine dependency induced by SMARCA4/2-loss. (**Nature Communications, accepted**)

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