

【Grant-in-Aid for Scientific Research (S)】

Broad Section I



Title of Project : Anti-cancer therapies aiming for cure through inhibiting tumor-specific responses to environmental fluctuation

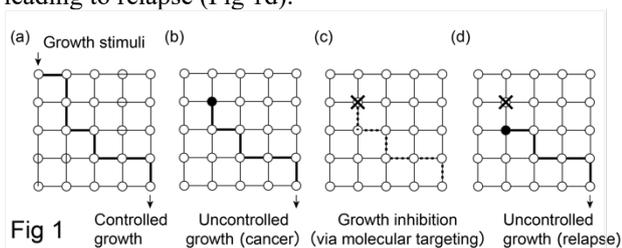
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Research Project Number : 19H05655 Researcher Number : 30184493

Keyword : Stress Response, Cancer Progression

【Purpose and Background of the Research】

Precision medicine based on molecularly targeting anti-cancer drugs has been revolutionized the strategy in cancer therapeutics. One drawback is, however, relapse of cancer cells resistant to the cognate medicine is not infrequent. Molecular targeting inhibits specific signaling molecules, activated by mutations (driver mutations, Fig 1a and b), thereby halt the autonomous cell proliferation (Fig 1c). However, cancer cells show genetic instability, which generates numerous random mutations in the genome. Accordingly, cells possessing a second driver mutation that bypasses the molecular targeting drug arises in time, leading to relapse (Fig 1d).



This argument led to a conclusion that to achieve cure without relapse in treating cancer patients, we need to target the system that uniquely enables cancer cells to undergo malignant progression, in addition to the molecular targeting towards driver genes.

【Research Methods】

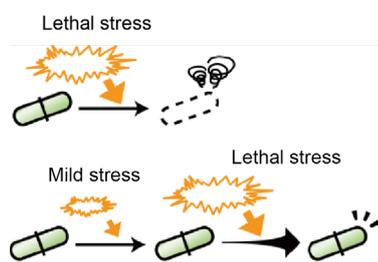


Fig 2 Acquired Tolerance

equips cells with resistance to a following lethal stress, using genetic screening in fission yeast. We will investigate to test whether tumors depend on acquired tolerance for their progression. If yes, we will exploit the dependence to develop novel cancer therapeutics.

We have previously investigated how cells respond to non-lethal mild stress. Specifically, we have revealed molecular mechanisms of acquired tolerance (Fig 2), a widely observed phenomenon where a preceding mild stress

Normal tissues in organisms are maintained under constant environment thanks to homeostasis. However, tumors are not benefitted by it, and accordingly are exposed to constant environmental fluctuation, such as those of oxygen and nutrient concentrations. As such, responses to non-lethal stresses are vital to tumors in maintaining their viability. This research will give a basic framework in targeting acquired tolerance as a novel strategy to develop cancer treatment aiming at cure.

【Publications Relevant to the Project】

• Chujo, M., Tarumoto, Y., Miyatake, K., Nishida, E., and Ishikawa, F. (2012). *J Biol Chem* 287(28), 23440-23450.

【Term of Project】 FY2019-2022

【Budget Allocation】 128,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.fish.lif.kyoto-u.ac.jp/en/home_en.html

【Expected Research Achievements and Scientific Significance】