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Cancer Acquired Resistance: A New Lesson from Chronic Myelogenous Leukemia

WenYong Chen*

Department of Cancer Biology, Beckman Research Institute, City of Hope, Duarte, CA 91010, USA

Despite decades of research and improvement of our understanding, the mechanisms of cancer, progress of cancer treatment has been slow. Targeted therapy is the most important advancement in cancer treatment by specifically inhibiting cancer-causing events, which improves the outcome of several types of human cancer in recent years [1]. However, targeted therapy is generally short-lived as cancer cells rapidly develop resistance (acquired resistance) against the treatment, resulting disease relapse. Acquisition of genetic mutations is a major mechanism underlying the resistance with different molecular targets in a variety of cancers including Chronic Myelogenous Leukemia (CML), lung, colon, breast and gastrointestinal cancers [1]. The conventional explanation is that rare pre-existing mutations formed through random mutagenesis may be selected for resistance under chemotherapy. Indeed, certain cancer patients do harbor detectable resistant mutations before targeted therapy [2-4]. However, what is not known is whether those rare pre-existing mutations solely account for the entire mutation load observed in patients and their relapse. This increasingly becomes a concern given that the majority of patients, for example CML, do not harbor detectable resistant mutations before treatment [5,6]. Although one could always blame the sensitivity of mutation detection methods, mechanistically, we know very little about how resistant mutations are actually acquired during cancer therapy.

CML is a fatal blood malignancy caused by oncogenic transformation of bone marrow hematopoietic stem cells as a result of chromosomal translocation t(9;22) that produces BCR-ABL fusion tyrosine kinase. CML is the first human cancer successfully treated by targeted therapy with tyrosine kinase inhibitor imatinib [7], and it continues its legend as a model disease for studying cancer drug resistance. Treatment with imatinib results in 5-year survival of most chronic phase CML patients [8], but has only short-term effect on advanced phase CML patients who frequently relapse with acquisition of BCR-ABL kinase domain mutations [2,9,10]. Yuan et al. [11] has recently established a novel model of CML acquired resistance using a blast crisis CML cell line KCL-22. Surprisingly, they found that CML cell relapse does not have to depend on pre-existing mutations and that most, if not all, BCR-ABL mutations are acquired *de novo* in response to imatinib treatment. This finding reveals a previously unrecognized way of mutation acquisition perhaps as a consequence of cancer cells' robust response to therapeutic stress. A new hypothesis has been proposed that *de novo* mutation acquisition in response to therapeutic stress can work independently or in conjunction with selection of pre-existing mutations to promote faster relapse in patients [5]. If proved true in human, this would have significant impact on cancer treatment and management.

The KCL-22 cell model provides an excellent tool to dissect molecular pathways for acquired resistance in CML. Using this model, Wang et al. [12] showed that the mammalian stress-response gene sirtuin 1 (SIRT1) is a critical factor for promoting acquisition of genetic mutations of BCR-ABL. SIRT1 is a protein lysine deacetylase that regulates multiple cellular functions including DNA damage repair and cell survival under stress [13]. SIRT1 is activated by BCR-ABL transformation of hematopoietic stem/progenitor cells and promotes leukemogenesis, and it renders CML stem cells refractory to imatinib treatment [14,15]. SIRT1 promotes *de novo* acquisition of BCR-ABL mutations for drug resistance in CML cells in association with the ability of SIRT1 to enhance error-prone non-homologous end joining DNA damage repair through deacetylating Ku70, a central factor for such repair [12]. Inhibition of homologous recombination repair factors NBS and RAD51 also suppresses BCR-ABL mutations, but apparently impacting non-homologous repair activity. This study provides the first evidence that resistant mutation acquisition is tied with error-prone DNA repair in human cancer cells.

In another study, Yuan et al. [16] used the same model to show that the process for acquisition of resistant BCR-ABL mutations is accompanied by mitotic crisis of CML cells under imatinib treatment. This mitotic crisis is mediated by reduction of mitotic kinase Aurora A gene expression when BCR-ABL kinase activity is inhibited by imatinib, causing cell cycle arrest at G2/M. Further inhibition of Aurora A activity by small molecule inhibitors or gene knockdown enhances mitotic crisis and stimulates apoptosis, thus preventing mutation acquisition to be completed and CML acquired resistance.

The above studies shed new insight of acquired resistance through genetic mutations, and provide proof-of-principle that at least certain forms of mutation acquisition under therapeutic stress are controllable and preventable. This contrasts the long-time doctrine that pre-existing mutations underlie acquired resistance and we have to passively develop more and more potent drugs to fight off unpredictable mutations when they emerge. The new discovery may change our future treatment of cancer by seeking active approaches to prevent or reduce mutation acquisition and extend remission. SIRT1 or Aurora A inhibitors could be deployed for such a purpose even though they target at different steps of BCR-ABL mutation acquisition. With better understanding of pathways of cancer acquired resistance, more novel therapeutic options would become available to overcome resistance.

In addition, identification of the stress response gene SIRT1 in mutation acquisition opens another door to explore how endogenous or environmental stress may contribute to or stimulate formation of "pre-existing" mutations, which is important to understand cancer evolution under stress. This becomes relevant as many cancer patients have gone through other treatments before they are given targeted therapy. Undoubtedly, continued studies in this area will help us

***Corresponding author:** WenYong Chen, Department of Cancer Biology, Beckman Research Institute, City of Hope, 1500 East Duarte Road, Duarte, CA 91010, USA, Tel: 626-301-8911; Fax: 626-471-7193; E-mail: wechen@coh.org

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better understand the process of acquired resistance, and create new approaches to improve therapeutic outcomes of cancer treatment.

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