Synthetic Lethality as a Promising Approach for Targeted Cancer Prevention

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Carcinogenesis is recognized as a multistep process. It occurs over a relative long span of time, which offers intervention opportunities for cancer prevention [1]. Using drugs to prevent cancer rather than treat cancer is the major research goal in the field of ‘chemoprevention’. Tremendous research efforts have been devoted toward using natural, synthetic or biological agents to prevent, suppress or delay the initiation and/or the progression of premalignant cells to cancer [1]. However a big challenge for effective cancer prevention is to identify chemoprevention agents with demonstrable efficacy and safety for healthy general population [2].

The process of carcinogenesis requires a series of genetic/epigenetic changes that transform normal cells to premalignant cells, then to malignant cells, and finally in some cases to metastatic cells [3]. With our exponentially increased knowledge of cancer genome landscapes via next generation sequencing technologies, it has been increasingly recognized that an important way to potentially reduce cancer deaths in the future is to improve cancer prevention based on our understanding of the cancer genomic information [4]. Cancer treatment is in the process of evolving from the conventional ‘one-size-fits-all’ approach to a personalized approach, in which patients are treated according to their genetic makeup. Can we conduct personalized cancer prevention with chemopreventive agents based on the genetic risk factors in population? The answer to this question requires the discovery of targeted cancer prevention strategies that can selectively eradicate premalignant cells with minimal toxicity to normal tissues by targeting the genetic vulnerability in premalignant cells.

Synthetic lethality is one of the most promising approaches for developing targeted cancer prevention strategy. Synthetic lethality involves the genetic interaction between two genes and pathways. The inhibition of either gene or pathway alone has no effect on cell viability, but the simultaneous inhibition of both genes or both pathways lead to cell death [5]. The goal of using synthetic lethality as a targeted cancer prevention approach is to identify agents that specifically kill premalignant cells with defined genetic alterations while leaving normal healthy cells unaffected. A recent study demonstrated the feasibility, efficacy and potential tolerability of this synthetic lethality approach for colorectal cancer chemoprevention in an in vivo preclinical setting [6].

Adenomatous polyposis coli (APC) is a tumor suppressor protein. Germ line mutations of this gene cause a premalignant disease, familial adenomatous polyposis (FAP), which usually becomes malignant. Thus it is of clinical importance to develop effective chemopreventive strategies for patients with APC mutations and FAP. In a recent study, combination of TNF-related apoptosis-inducing ligand (TRAIL) and retinyl acetate (Rac) leads to a synthetic lethality in APC -deficient intestinal adenoma cells [6]. In normal cells high expression of cellular FLICE-like inhibitory protein (c-FLIP) forms an internal block for TRAIL-induced apoptosis. APC protein acts as a negative regulator of the Wnt signaling pathway, which is involved in multiple cellular functions including transcriptional activation, cell migration and adhesion and apoptosis. In APC-deficient premalignant cells, β-catenin, a major player of the Wnt signaling pathway is activated. Activation of β-catenin leads to a decrease of c-FLIP expression, which eliminates the internal block on the TRAIL pathway. Thus APC deficiency removes a critical block for TRAIL-induced apoptosis. APC protein acts as a negative regulator of the Wnt signaling pathway, which is involved in multiple cellular functions including transcriptional activation, cell migration and adhesion and apoptosis. In APC-deficient premalignant cells, β-catenin, a major player of the Wnt signaling pathway is activated. Activation of β-catenin leads to a decrease of c-FLIP expression, which eliminates the internal block on the TRAIL pathway. Thus APC deficiency removes a critical block for TRAIL-induced apoptosis, which results in a synthetic lethal interaction between TRAIL/RAC and APC deficiency in premalignant cells [6]. Later a similar concept was tested in mutant KRAS premalignant cells, which contain reduced c-
FLIP expression [7]. These studies provide a proof-of-principle that synthetic lethality can be used as a targeted cancer prevention strategy to eradicate premalignant cells with defined genetic alterations [8].

Therefore, it is a key question to identify genes or drugs that have a synthetic lethal interaction with genes or pathways altered in premalignant cells, which can provide us with opportunities to develop synthetic lethality-based targeted cancer prevention. Selective killing of BRCA-deficient breast cancer cells by poly(ADP-ribose) polymerase (PARP) inhibitors highlighted that DNA repair pathways can be exploited to discover new synthetic lethal interactions for cancer prevention [9,10].

Breast cancer susceptible proteins BRCA1 and BRCA2 are required for DNA double-strand break (DSB) repair by the error-free repair of homologous recombination (HR) through gene conversion [11-13]. Cells deficient in BRCA1 or BRCA2 have been found to be 100-1000-fold more sensitive to inhibitors of poly-ADP-ribose polymerase (PARP) than normal cells [9,10]. The underlying mechanism stems from a delicate synthetic lethal effect. PARP is an enzyme that facilitates repair of single-stranded breaks (SSB). In normal cells, DNA damage generated by PARP inhibitors is well tolerated because of functional compensation from the HR repair pathway. In contrast, HR repair defective cancer cells, such as BRCA1 or BRCA2 deficient-cells, are unable to cope with this increased DNA damage and thereby exhibit hypersensitivity to PARP1 inhibitors [14]. This finding provides a molecular basis to exploit induced cancer-specific synthetic lethality by PARP1 inhibitors not limited to BRCA1 or BRCA2 deficient-cells, but more broadly applied to all HR deficient cancer cells. BRCA1 and BRCA2 are frequently mutated in familial breast cancer and ovarian cancer patients. Currently, multiple studies are testing the preventive effects of PARP inhibitors in preventing BRCA-associated breast and ovarian cancers.

It is worth noting that using synthetic lethality as a promising approach for cancer prevention might be more readily exploited for germline mutations that predispose to carcinogenesis such as mutations of APC and BRCA genes described above. In contrast, targeting somatic mutations present in premalignant lesions could be more challenging. Firstly, the common or frequent mutations in premalignant lesions are not well-defined. The next generation sequencing technology can be a promising approach to identify somatic aberrations in premalignant lesions, which will help establish effective genetic interactions to develop synthetic lethality-based interventions. Importantly, premalignant cells with a limited number of genetic alterations represent the most efficient stage during carcinogenesis for targeted intervention. Thus targeted chemoprevention using synthetic lethality-strategies can be very effective at very early stages of tumorigenesis. Secondly, in order to determine the efficacy of targeted chemoprevention, it is essential for us to have an effective screening tool to monitor the progression of premalignant diseases. Thus, to develop effective screening methods and to identify biomarkers are the key steps for the success of this targeted prevention strategy.

In summary, here we presented studies to show that it is indeed possible to use synthetic lethal interactions to develop effective targeted cancer prevention strategies. Instead of searching for a universal chemoprevention drug for large populations of people at relatively low risk, one promising direction of chemoprevention research in future is to identify intervention strategies for subpopulations at high risk of developing cancer by targeting the genetic alterations in premalignant lesions, such as using a synthetic lethality as a guide for drug discovery.

References