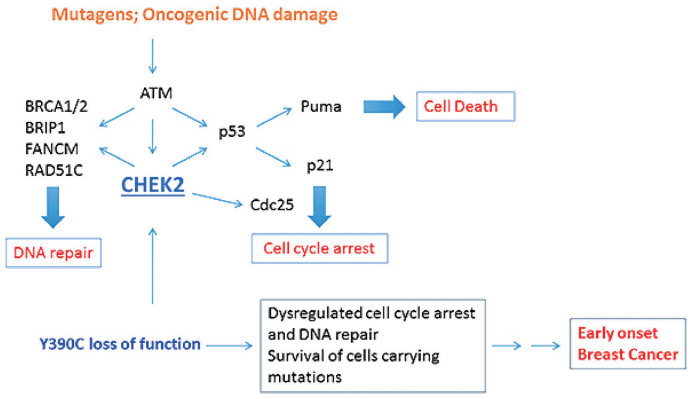
Life Science

# Novel CHEK2 Mutation Identified Potentially Responsible for Early Onset of Breast Cancers in Chinese Population

Breast cancer is the most frequently diagnosed cancer and the second deadly tumor in females worldwide. On average, breast cancer patients in China are diagnosed of this disease 10 years earlier than their counterparts in US and Europe, and a higher percentage of them are diagnosed of this at 40 or earlier than in Caucasians. However, unlike in Caucasians, the occurrence of mutations in BRCA-1 and/or BRCA-2, which are widely believed to lead to the production of a susceptible protein responsible for the onset of inherited breast cancers, is low in Chinese population; so is that of previously reported mutations in Checkpoint kinase 2 (CHEK2) germline. This suggests that early onset of breast cancer in China might be connected with other hereditary factors.

In search for alternative genetic alleles associated with early onset of breast cancer in China, DING Hongyu and his fellow PhD students from a research group led by Prof. JIANG Hai at the Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Sciences, CAS identified a mutation at a novel locus, namely CHEK2 Y390C, in young, highly risk breast cancer patients in China, in collaboration with Changhai Hospital under the Second Military Medical University of China. They further verified that this mutation existed in 12 out of 150 patients (8.0%), contrasted with only 2 out of 250 in healthy controls (0.8%). Four of the Y390C carriers also had family history of breast and/or ovarian cancers, and a trend identified in Y390C carriers suggested that they might tend to develop breast cancer early, before 35 years of age. These facts indicate that the CHEK2 Y390C mutation is probably a novel hereditary factor specific for Chinese breast cancer patients.

CHEK2 is a central effector of cell's response to DNA damage. Upon DNA damage, CHEK2 will phosphorylate BRCA2, p53 and CDC25 to orchestrate DNA repair and cell cycle arrest, as well as cell death when the damage is beyond repair. Functional analysis suggests that the CHEK2




This picture illustrates that CHEK2 Y390C mutation leads to DNA repair dysfunction, deregulated cell cycle checkpoint; and that apoptotic response may help conserve mutations and therefore contribute to tumourigeneisis. (Image by courtesy of Prof. JIANG Hai's group)

Y390C mutation is deleterious as judged by the mutant protein's inability to inactivate CDC25A or to activate p53 after DNA damage. Cells expressing the CHEK2 Y390C mutant also show impaired p21 and Puma expression after DNA damage. Such deregulated cell cycle checkpoint Breast cancer is the most frequently diagnosed cancer and the second deadly tumor in females worldwide. On average, breast cancer patients in China are diagnosed of this disease 10 years earlier than their counterparts in US and Europe, and a higher percentage of them are diagnosed of this at 40 or earlier than in Caucasians. However, unlike in Caucasians, the occurrence of mutations in BRCA-1 and/or BRCA-2, which are widely believed to lead to the production of a susceptible protein responsible for the onset of inherited breast cancers, is low in Chinese population; so is that of previously reported mutations in Checkpoint kinase 2 (CHEK2) germline. This suggests that early onset of breast cancer in China might be connected with other hereditary factors.

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This study puts forward a new subject for breast cancer prevention, suggesting the need for early monitoring of breast cancer in the 0.8% Y390C carriers in Chinese population. It also suggests that novel therapeutic regimens should be considered for such breast cancer patients in clinics. Entitled "*A novel recurrent CHEK2 Y390C mutation identified in high risk Chinese breast cancer patients impairs its activity and is associated with increased breast cancer risk*", this study was published online in *Oncogene* on Jan 26, 2015.

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