The Fanconi anemia-BRCA pathway and chemoresistance of cancer cells.

The Fanconi anemia-BRCA pathway has emerged as an important pathway in cancer biology. Fanconi anemia (FA) is a rare genetic disease characterized by chromosomal instability, cancer-susceptibility and cellular sensitivity to interstrand DNA crosslink (ICL)-inducing agents. Sixteen FA genes have been identified (FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51, FANCP/SLX4 and FANCQ/XPF). The FA proteins and breast/ovarian cancer susceptibility proteins, BRCA1 and BRCA2, cooperate in a common pathway required for cellular resistance to ICL-inducing agents. This pathway is called the FA-BRCA pathway or FA pathway. The main function of the pathway is to coordinate multiple DNA repair mechanisms during ICL repair. Inactivation of this pathway in cancer cells can lead to sensitivity to anti-cancer ICL-inducing agents, such as cisplatin, while reactivation of this pathway is implicated in acquired resistance to ICL-inducing agents. Therefore, inhibition of the FA-BRCA pathway is an attractive therapeutic strategy to overcome DNA-crosslinker resistance of tumor cells.

In this talk, I will introduce what the FA-BRCA pathway is and how this pathway is inactivated in human cancer. I will also mention our finding that secondary BRCA1/2 mutations, which restore normal function of BRCA1/2 proteins, are involved in acquired drug resistance of BRCA1/2-mutated cancer.