DDX11 Helicase in Warsaw Breakage Syndrome, DNA Damage Response and Sister Chromatid Cohesion

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Chapter 8

Summary

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DNA duplication and distribution during cell division is tightly controlled. During S-phase of the cell cycle, every chromosome is identically synthesized and subsequently, two sister chromatids are created. The sister chromatids are kept together until anaphase, where they are separated and pulled towards opposite poles of the cell. This process, which is very crucial for each daughter cell to have the correct set of chromosomes, called sister chromatid cohesion. A ring form protein complex, called cohesin, is responsible for the cohesion between the two sister chromatids. Cohesin complex is composed of three core subunits: SMC1A, SMC3 and RAD21/Scc1 and two HEAT-repeats containing proteins: STAG1/STAG2 and PDS5A/PDS5B.For proper sister chromatid cohesion, cohesin needs to cooperate with multiple other proteins, such as NIPBL and MAU2 (responsible for cohesion loading), WAPL and PDS5 (associated with cohesin unloading), acetyltransferases ESCO1 and ESCO2 (establish cohesion), DDX11 (involved in cohesion maintenance). Mutations in a number of these components and regulators cause several related syndromes, called cohesinopathies (see chapter 2). For examples, mutations in SMC1A, SMC3, RAD21, STAG2 and NIPBL cause Cornelia de Lange syndrome (CdLS), mutations in ESCO2 and DDX11 are respectively responsible for Roberts Syndrome (RBS) and Warsaw Breakage Syndrome (WABS). Besides, cohesin mutations play an important role in the development of several types of cancer and understanding the mechanisms will be very important for future treatment of tumors with impaired cohesion. In this thesis we broaden our understanding regarding general understanding of sister chromatid cohesion.

In chapter 1, we introduce the general understanding of sister chromatid cohesion and the most recent findings. In chapter 2 we discussed the present understanding of the different cohesinopathy syndromes, including clinical features, genetic causes, underlying biology and their possible links with cancer predisposition. In chapter 3 we showed that lymphoblasts derived from WABS, RBS and Fanconi Anemia (FA), which is clinically related to WABS and RBS, are sensitive to inhibition of PARP pathway. Specially, DNA helicases DDX11 and FANCM were identified as determinants of PARP inhibitor response. Since PARP inhibitors are applied in the treatment of *BRCA*-mutated breast and ovarian cancer, identifying additional determinants of PARP inhibitor sensitivity would extend their utility in cancer therapy. In search to find additional synthetic lethal networks in cohesion defective cancer cells, we discovered in chapter 4 synthetic lethality between DDX11 and several subunits of the Anaphase Promoting Complex or Cyclosome (APC/C). In addition, we identified that a newly synthesized APC/C-inhibiting drug, Apicin can selectively kill cohesion defective cancer cells. These findings are important for developing new cancer therapy, which only targets cohesion defective cancer cells. Additionally in chapter 5, we also showed synthetic lethality between DNA helicase DDX11 and SMC3 acetyl transferases ESCO1/ESCO2. WABS derived cells rely on ESCO2, but not ESCO1 for residual sister chromatid cohesion, cellular growth and survival. Also, we demonstrated that DDX11 required for normal replication fork progression without clearly affecting SMC3 acetylation.

In chapter 6 we demonstrated different new WABS patients, with *DX11* containing a null and a weakened allele that encodes an unstable but functional DDX11 protein. We strengthened our findings by creating DDX11-mutated RPE1 cells, where DDX11 knockout is responsible for reduced cell growth in a p53-dependent manner. Also, we showed that specially DDX11 helicase activities are required for sister chromatid cohesion by possibly dissolving G-quadruplex (G4) structures, created during DNA replication. We exhibited that stabilization of G4 structures induces defective sister chromatid cohesion in normal cells and cellular lethality in DDX11-deficient cells. In conclusion, we proposed a model, where DDX11 helicase activity is important for maintaining genomic integrity through dissolving DNA secondary structures and preventing G4-induced breaks during DNA replication. Thus cohesion defects in WABS might result from either defective cohesin loading or excessive cohesin removal from broken replication forks to facilitate DNA repair.

In chapter 7 we summarized and discussed studies described in the thesis and proposed some future perspectives. Overall, the work presented in this thesis is a step forward toward understanding how sister chromatid cohesion functions and its importance in human development and carcinogenesis. Furthermore, our work provides ground for finding out how cohesion defects in tumors can be exploited to develop new anti-cancer therapies (see box 1 in chapter 7).