CHD1 loss sensitizes prostate cancer to DNA damaging therapy by promoting error-prone double-strand break repair

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Background
Homozygous deletion of the chromatin remodeler *CHD1* is a common structural alteration found in the human prostate cancer genome. *CHD1* deleted tumors are characterized by high numbers of intrachromosomal rearrangements suggesting underlying defects in DNA double-strand break (DSB) repair. Here we investigate whether this subclass of prostate cancer has a defective DNA damage repair, is sensitive to DNA damaging compounds and whether this genomic alteration could be used as biomarker to stratify patients.

Methods
To study the role of *CHD1* deletions *in vivo* and *in vitro* we developed a novel genetically engineered mouse model with prostate-specific loss of *Chd1*, CRISPR/CAS9 engineered human prostate cancer cells with loss of *CHD1* as well as patient-derived organoids (PDOs) with and without *CHD1* deletions. We evaluated the effect of the deletion in these models on DNA DSB repair competence, global chromatin structure, cell cycle regulation and drug sensitivity (carboplatin, olaparib, irradiation). Finally, we treated a *CHD1* deleted castration-resistant prostate cancer (CRPC) patient with carboplatin.

Results
Here we show that CHD1 loss causes increased sensitivity to irradiation-mediated DNA damage in mES cells and the mouse prostate. It is also synthetic lethal with DNA damaging agents such as carboplatin or olaparib. We confirmed these responses in preclinical human models with CHD1 loss and in a patient with CRPC. Mechanistically, CHD1 maintains euchromatin, binds components of the DNA damage repair machinery and regulates stability of 53BP1. Thereby, CHD1 controls the choice between error-free and error-prone DNA double-strand break repair. Loss of CHD1 increases heterochromatin formation, impairs error-free homologous recombination (HR) mediated DNA double-strand break and causes a cellular dependence on error-prone non-homologous end joining (NHEJ). We validated these findings clinically in a CHD1 deleted CRPC patient, whose PDO was sensitive to PARP-1 inhibition. The patient showed a radiological response accompanied with dramatic decreases in PSA and circulating tumor cell counts.

Conclusions
In summary, we report that CHD1 loss leads to changes in DNA damage response. Importantly, CHD1 loss is associated with an increased sensitivity to PARP inhibition and anticancer drugs that induce DNA intercross-strand links including carboplatin.

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