"the siDNA: a new method to sensitize radioresistant tumors to irradiation"

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Cells process foreign DNA as their own, they transcribe, replicate, recombine and repair incoming DNA whatever its origin is. We used this property to lure the cells and hijack the repair complex far from its cognate substrate, the damaged DNA. For this purpose, we synthesized short inhibiting DNA molecules (siDNA) that mimic DNA damage. We show that, in vitro, the siDNA mimicking DNA double-strand breaks (called Dbait) specifically bind to the DNA-dependent protein kinase (DNA-PK) repair complex and activates DNA-PK's but not ATMs' nor ATRs' kinase activity. The histone variant H2AX is highly phosphorylated in a strictly DNA-PK-dependent manner as a consequence of Dbait transfection. The pattern of H2AX phophorylation in cells transfected by Dbait is different of the foci organization observed when H2AX phosphorylation is triggered by irradiation.

Dbait transfection inhibits non-homologous recombination and DNA repair by non-homologous end joining (NHEJ) and, as a consequence, increases cell death in response to irradiation. In vivo, Dbait treatment induces regression of tumors in mice xenografted with various radio-resistant tumors (HNCC, Melanoma, Glioblastoma). The tumor growth control is dose-dependent of Dbait administered. Administration of Dbait before irradiation greatly improve radiotherapy efficiency.