The Molecular Mechanism of PRAK Regulating DNA Damage Repair and Its Role in Breast Cancer

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Background

DNA damage plays a critical role in breast cancer, induced by both endogenous and exogenous factors. Abnormal repair mechanisms, such as homologous recombination repair (HRR) and non-homologous end joining (NHEJ), result in genomic instability and the accumulation of mutations, thereby driving cellular malignant transformation. DNA damage also promotes tumor progression by activating inflammatory pathways and modulating the immune microenvironment, serving as a key basis for breast cancer development and treatment resistance.

Core Findings

PRAK (p38-regulated/activated protein kinase) is highly expressed in breast cancer and significantly correlates with poor patient prognosis and reduced survival rates. In vitro and in vivo experiments demonstrate that PRAK deficiency sensitizes tumor cells to PARP inhibitors and impairs DNA double-strand break (DSB) repair capacity, leading to defects in the homologous recombination (HR) pathway. Molecular Mechanism: Through affinity chromatography, mass spectrometry, and co-immunoprecipitation, PRAK was confirmed to directly interact with FOXO3 in vitro and in vivo. DNA-damaging agents (PARP inhibitors) induce nuclear accumulation of FOXO3, promoting the interaction between PRAK and FOXO3 within the nucleus. RNA-seq analysis revealed that BRCA1 is a key target of PRAK. PRAK deficiency reduces FOXO3 nuclear localization and inhibits its binding to the BRCA1 promoter, thereby downregulating BRCA1 expression. In vivo validation demonstrated that PRAK deficiency enhances the sensitivity of mouse xenografts to DNA-damaging agents.

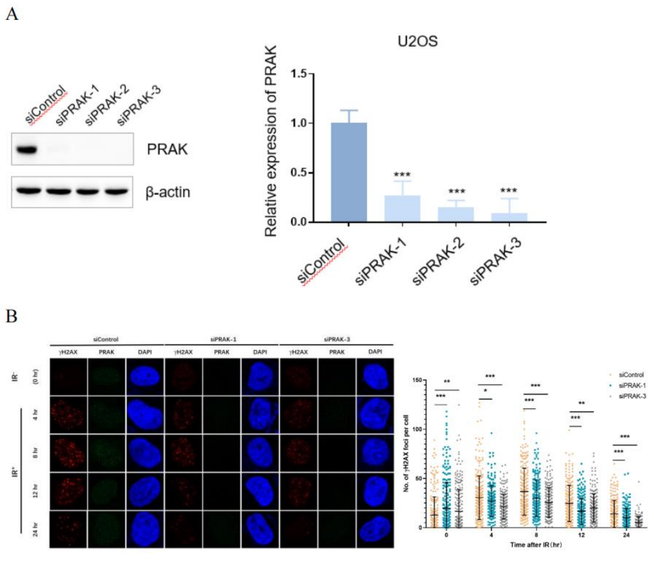


Figure 1. Knockdown of PRAK expression impairs the DNA damage response in U2OS cells.

A. Western blot and RT-PCR were employed to validate the silencing efficiency of siRNA.
B. PRAK expression was knocked down in U2OS cells using siRNA. After treatment with 4Gy IR (to induce DNA damage), cells were collected at 0, 2, 4, 8, 12, and 24 hours, and the total number of γH2AX foci was detected by immunofluorescence. The right panel shows the statistical graph, with the number of cells counted (n > 200). Statistical significance was analyzed by ANOVA, and asterisks indicate the significance levels between different groups.

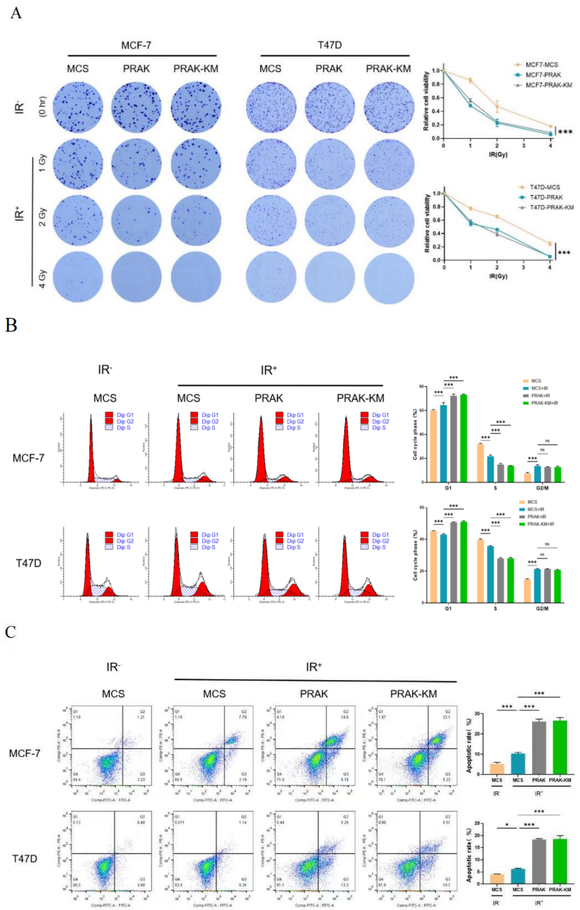


Figure 2. PRAK enhances the radiosensitivity of breast cancer cells.

A.Clonogenic survival assays were performed to assess the radiosensitivity of control (MCS), PRAK-overexpressing, and PRAK-KM (kinase-dead) MCF7 and T47D cells following exposure to varying doses of radiation (0, 1, 2, 4 Gy). Cells were cultured for 12-14 days post-irradiation to allow for colony formation.
B. Flow cytometric analysis of cell cycle distribution in control (MCS), PRAK-overexpressing, and PRAK-KM MCF7 and T47D cells, either untreated (IR-) or at 48 hours after treatment with 4 Gy irradiation (IR+).
C. The effect of PRAK overexpression on radiation-induced apoptosis in MCF7 and T47D cells.

Conclusions

PRAK is upregulated in multiple human tumor tissues. PRAK deficiency inhibits tumor cell proliferation and sensitizes cells to DNA-damaging agents. PRAK participates in HR-mediated DNA damage repair in an enzyme activity-independent manner. PRAK interacts with FOXO3, influences FOXO3 nuclear localization to regulate DNA damage responses, and affects FOXO3 binding to the BRCA1 promoter to modulate BRCA1 transcriptional activation. PRAK deficiency enhances tumor sensitivity to DNA-damaging drugs. Collectively, this study reveals that PRAK promotes DNA damage repair by transcriptionally regulating BRCA1 expression through FOXO3, representing a novel regulatory mechanism by which PRAK maintains genomic stability via DNA damage repair. Targeting the PRAK/FOXO3/BRCA1 axis may serve as a potential therapeutic strategy to enhance the efficacy of DNA-damaging agents in cancer treatment. Our findings uncover the functions and molecular mechanisms of PRAK in cell proliferation and DNA damage responses, with potential clinical implications for breast cancer therapy.

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