



- Special comment -  
related to DNA damage response of  
BRCA1 and chemosensitivity

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## What made the difference?

Case 1 : TNBC with family history, T1cN3bM0

FEC/wPTX → **pCR** (with intraductal component)

embryo cryopreservation → pregnancy delivery / **healthy**

Case 2: TNBC, T2N1M0

FEC/wPTX → **PR**

Recurrence to ipsilateral breast & supraclavicular LNs

Phase I/II eriburin/oraparib → **PD**

carboplatin/S1 → **SD** → **PD** (liver metastasis)

gemcitabine

subtypes in TNBC? EMT?

other biological issues?



## **TN paradox: pCR vs non-pCR**

possibly due to differences in DNA repair capacity

**mild DNA repair failure → carcinogenesis**

**severe DNA repair failure → cell death**

**specifically failure in homology-directed repair  
(homologous recombination)**



## **TN paradox: pCR vs non-pCR**

possibly due to differences in DNA repair capacity

1) A current topic in basic research:

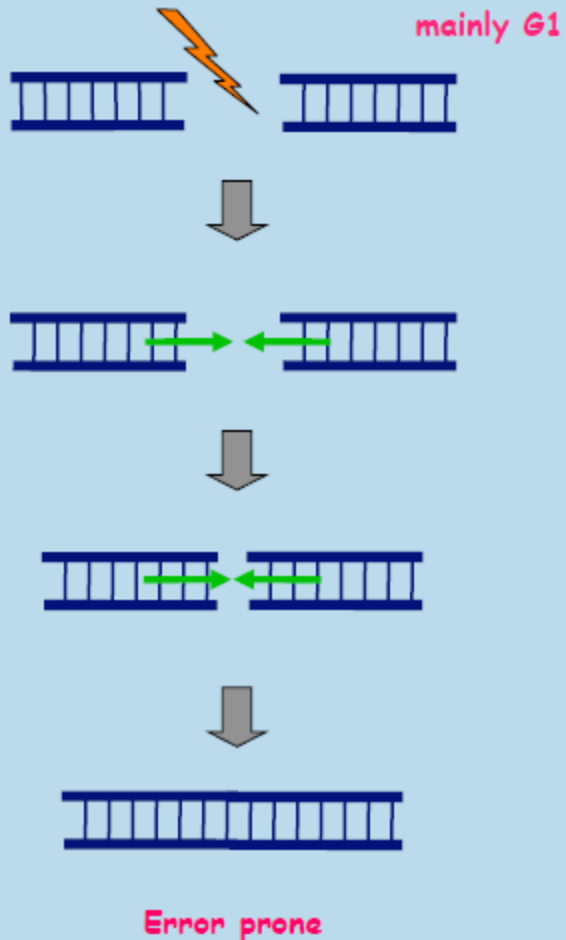
**additional 53BP1 failure**

2) A new finding:

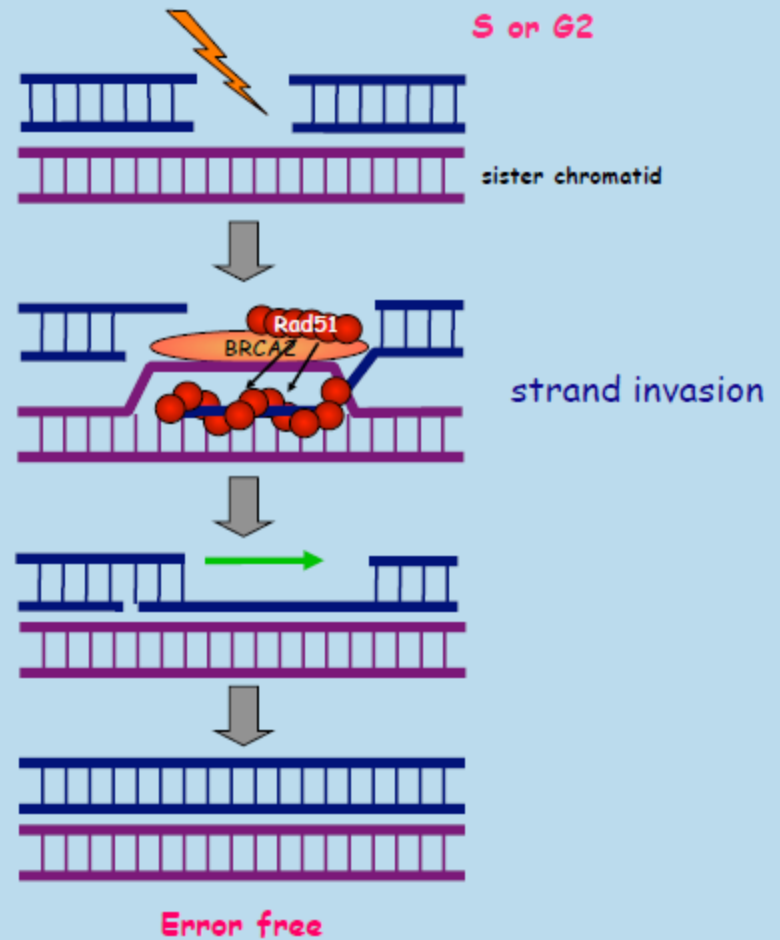
**a novel mechanism to retain BRCA1**

## Repair of DNA double-strand breaks

nonhomologous end joining  
(NHEJ)

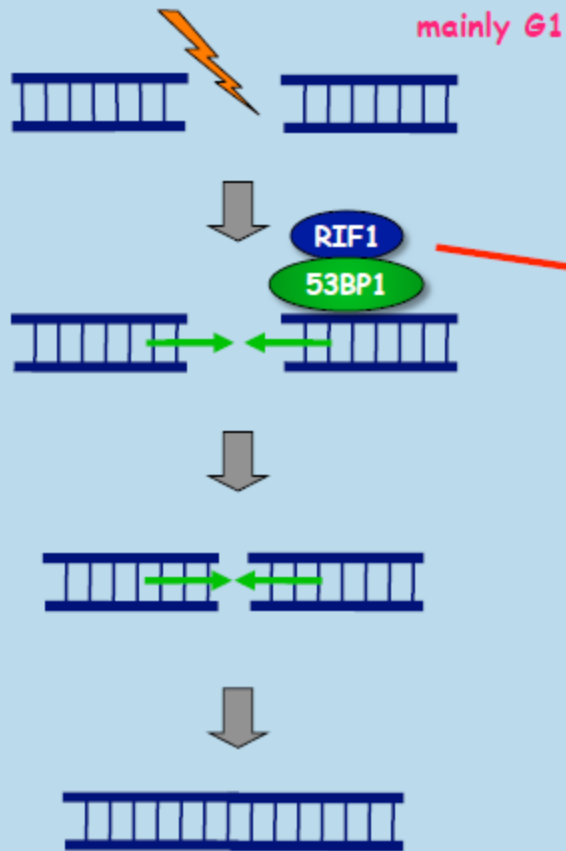


homology-directed repair  
(HDR)

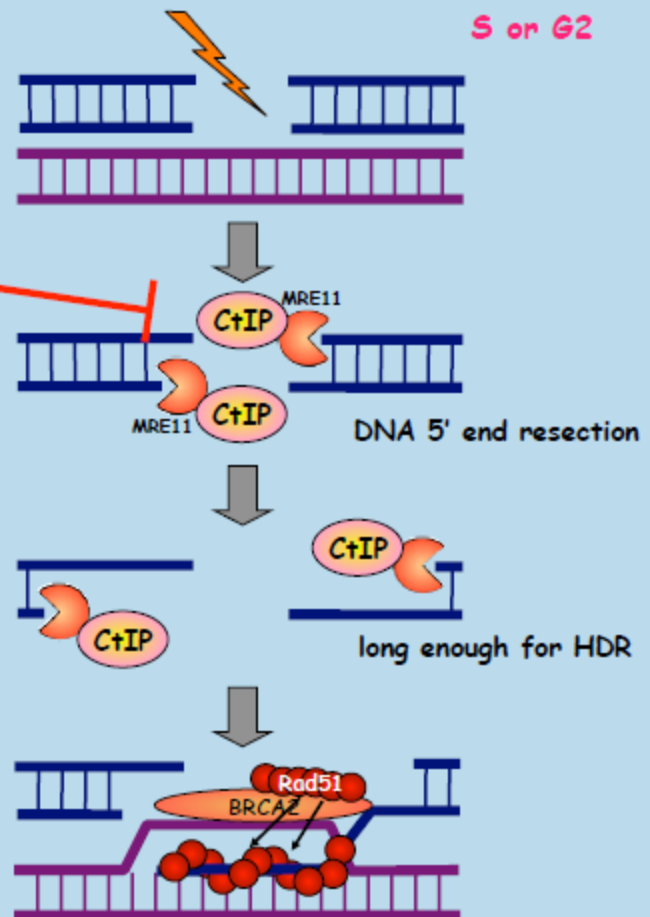


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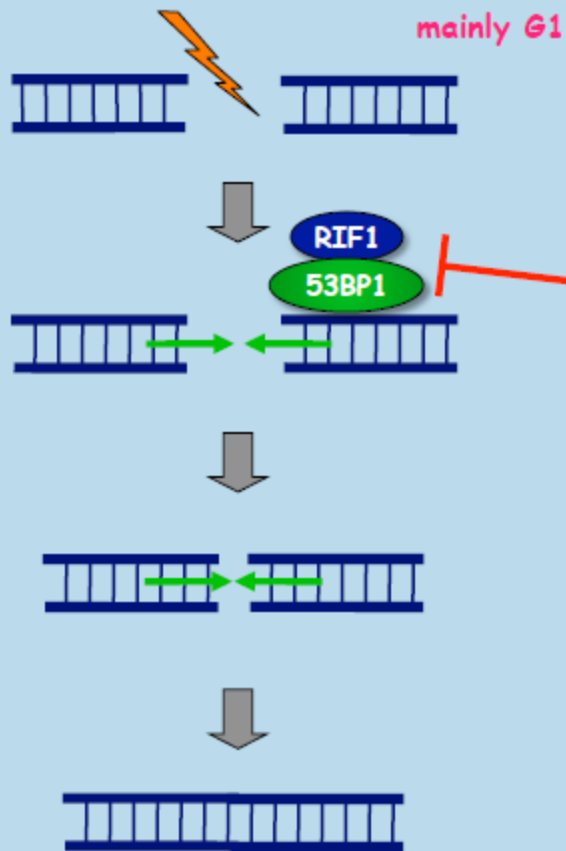


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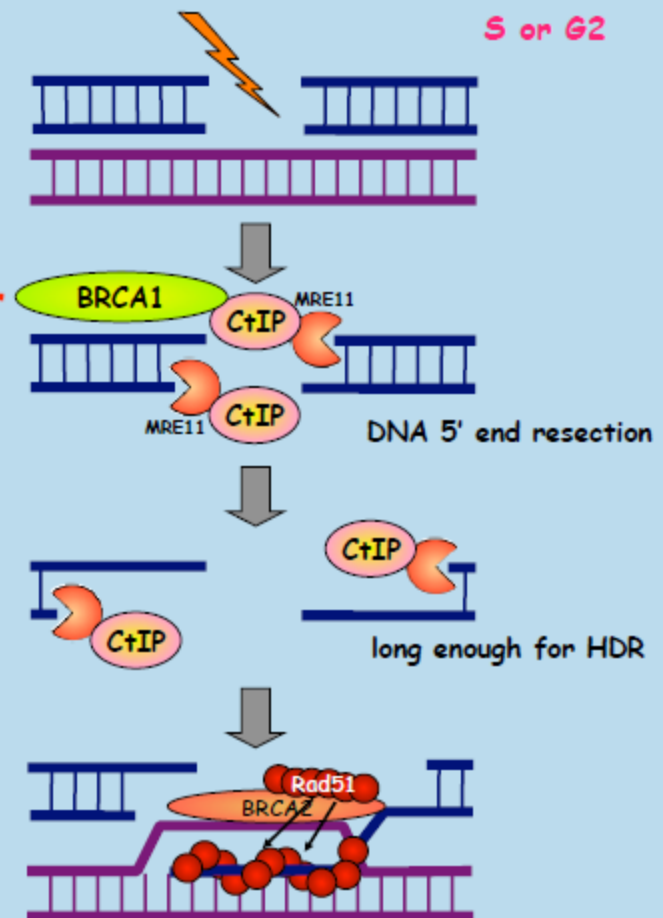


## Repair of DNA double-strand breaks

nonhomologous end joining  
(NHEJ)



homology-directed repair  
(HDR)



## Repair of DNA double-strand breaks



Embryonic lethality induced by Brca1 mutation can be rescued by 53BP1 deletion.

Cao, et al. 2009 Mol Cell

53BP1 loss rescues BRCA1 deficiency and is associated with TNBC.

Bouwman, et al. 2010 Nat Struct Mol Biol

53BP1 inhibits HDR in BRCA1 deficiency by blocking DNA end resection.

Bunting, et al. 2010 Cell

RIF1 inhibits DNA resection by CtIP, limits accumulation of BRCA1/BARD1 complexes

Zimmermann, et al. 2013 Science

RIF1 counteracts BRCA1-mediated DNA end resection.

Feng, et al. 2013 J Biol Chem

RIF1 blocks DSB resection to promote NHEJ, which is antagonized by BRCA1 in S phase.

Chapman, et al. 2013 Mol Cell

RIF1 is antagonized by BRCA1 and CtIP.

Escibano-Diaz, et al. 2013 Mol Cell



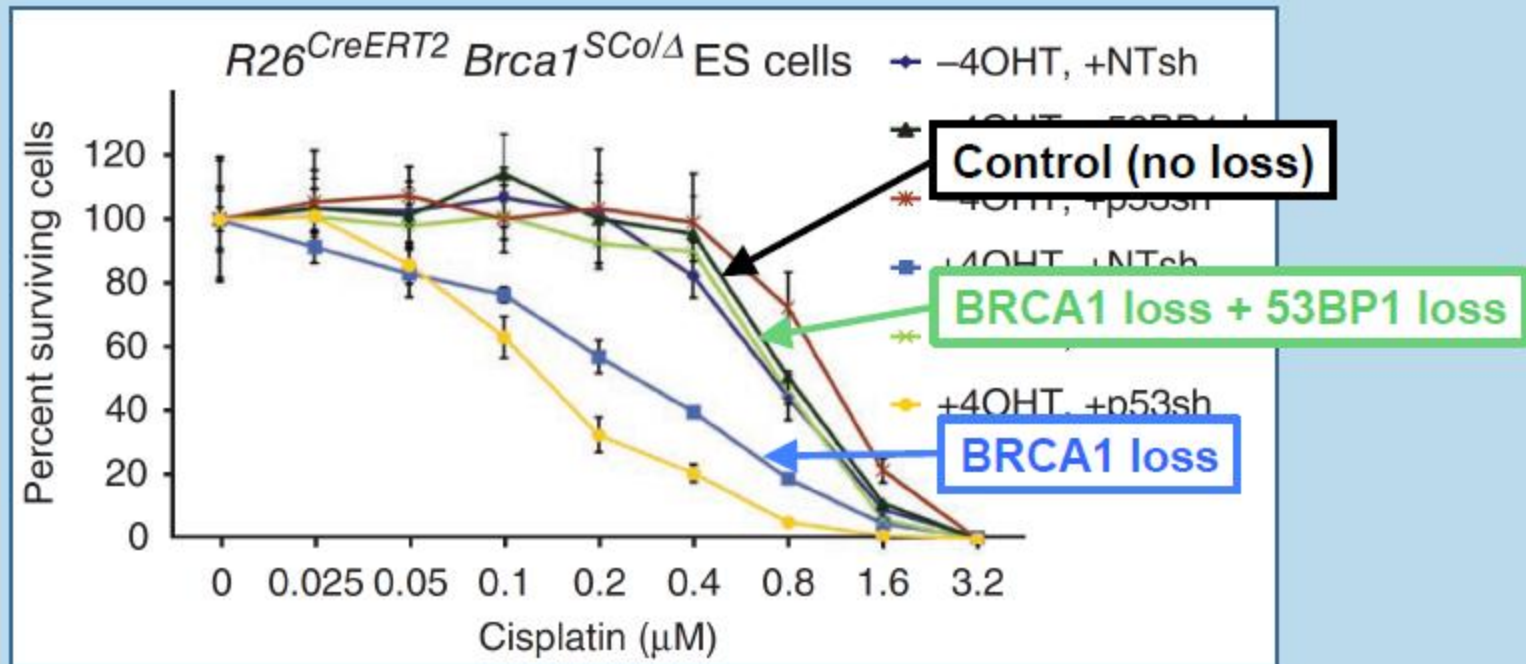
## 53BP1 loss rescues BRCA1 deficiency and is associated with TNBC.

**Table 2 Low 53BP1 expression correlates with triple-negative status (Yale cohort)**

Features	53BP1 expression			<i>p</i> <sup>a</sup>
	Total (%)	Positive (%)	Negative (%)	
Estrogen receptor				
Positive	243 (55)	239 (63)	4 (6)	
Negative	200 (45)	140 (37)	60 (94)	<0.0001
Progesterone receptor				
Positive	226 (51)	222 (59)	4 (6)	
Negative	217 (49)	157 (41)	60 (94)	<0.0001
ERBB2/HER2				
Positive	78 (18)	77 (20)	1 (2)	
Negative	366 (82)	303 (80)	63 (98)	<0.0001
Triple-negative (TN)				
Not TN	311 (70)	305 (80)	6 (10)	
TN	132 (30)	75 (20)	57 (90)	<0.0001

<sup>a</sup>Fisher's exact test.

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