Skills Circle

MECHANISM OF TUMOR CURE BY SINGLE DOSE RADIOTHERAPY

VARIAN ONCOLOGY SYSTEMS

Nuno Pimentel

June 2015

Champalimaud Foundation

VARIAN medical systems

Acknowledgement

Zvi Fuks

Scientific Director

The classical Model of Clinical Radiotherapy

- Tumor cure with single dose radiotherapy is not feasible because of biological, not just technical, limitations
- A fractionated approach is required to build up sublethal damage to a threshold that confers tumor stem cell lethality

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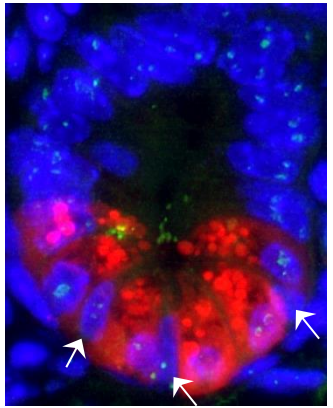
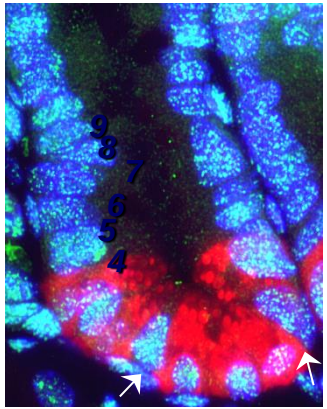
Basic Tenets of Tumor Radiobiology: The Single Target Model

- *Tumor stem cells are the relevant targets*
- *DNA DSB is the cellular lethal lesion*

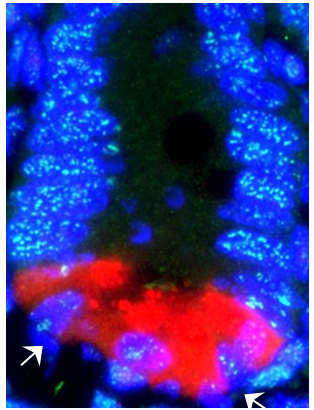
Lesion	Number / Gy / Cell
Double strand breaks (dsb)	40
Single strand breaks (ssb)	500-100
Base damage	1000-2000
Nucleotide damage	800-1600
DNA-DNA cross-links	30
Protein-DNA cross-links	150



Unirradiated Intestinal Crypt



1 hr post 12 Gy

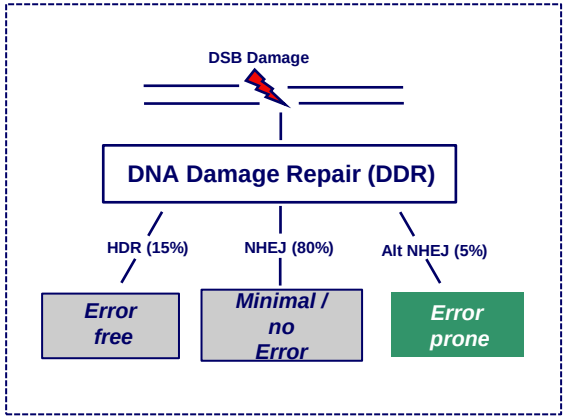


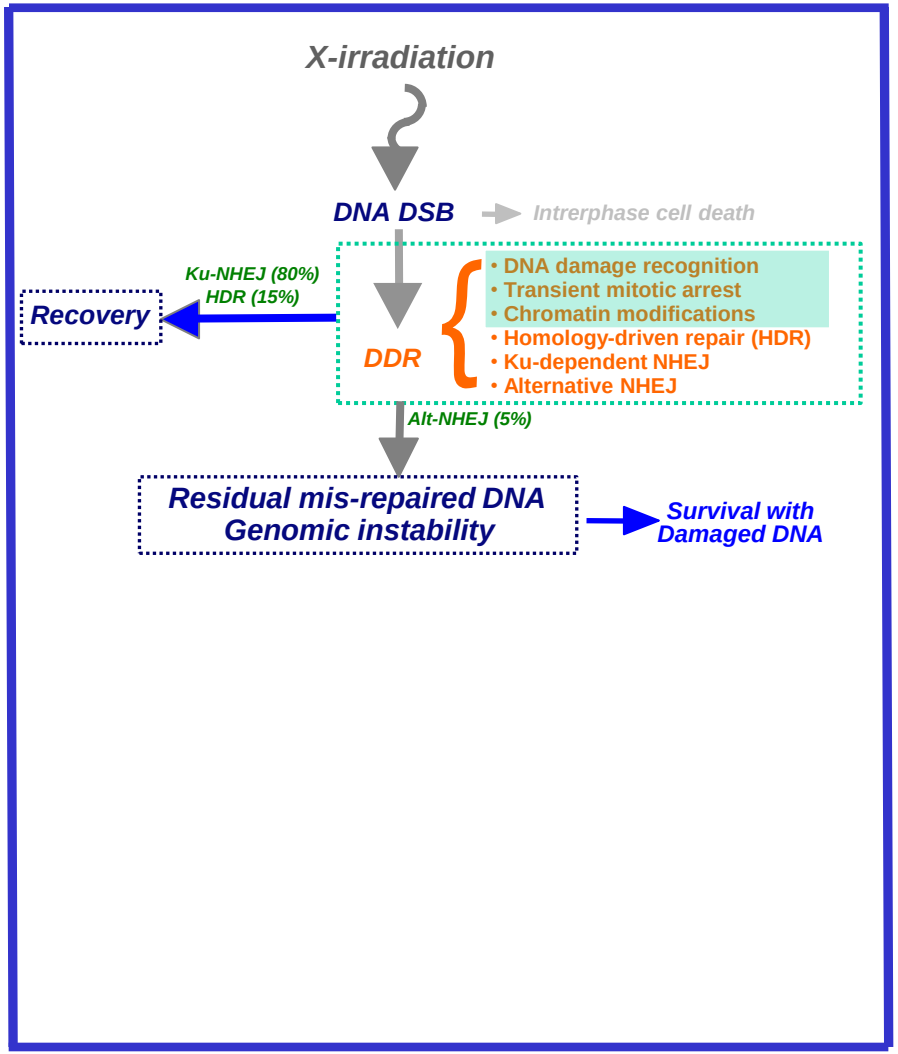
12 hrs post 12 Gy

Hua, Gastroenterology,143:1266, 2012

Basic Tenets of Tumor Radiobiology: The Single Target Model

- *Tumor stem cells are the relevant targets*
- *DNA DSB is the cellular lethal lesion*
- ***An acute DNA damage response (DDR) coordinates pathways of DSB repair***

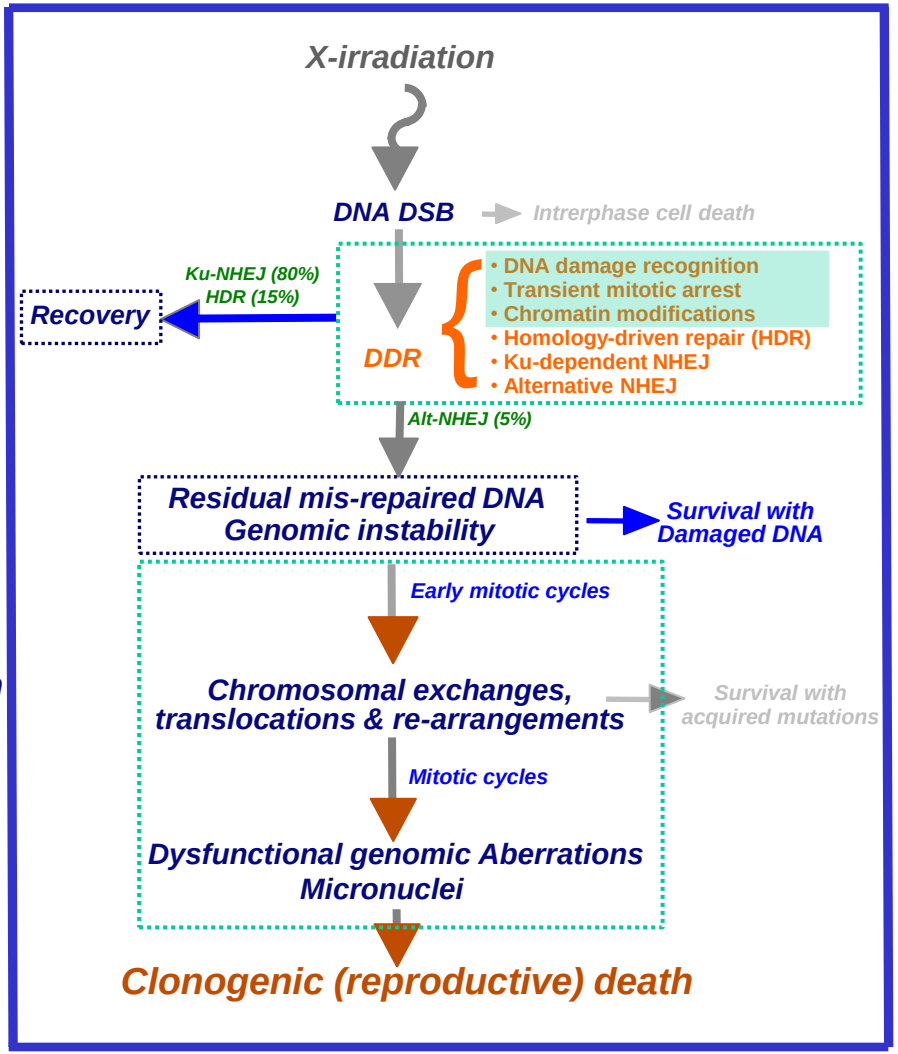




Basic Tenets of Tumor Radiobiology: The Single Target Model

- *Tumor stem cells are the relevant targets*
- *DNA DSB is the cellular lethal lesion*
- *An acute DNA damage response (DDR) coordinates pathways of DSB repair*
- ***The initial outcome of DDR is genomic instability, not tumor cure***
- ***Stem cell depletion and tumor cure result from conversion of misrepaired DSB into lethal chromosomal aberrations***

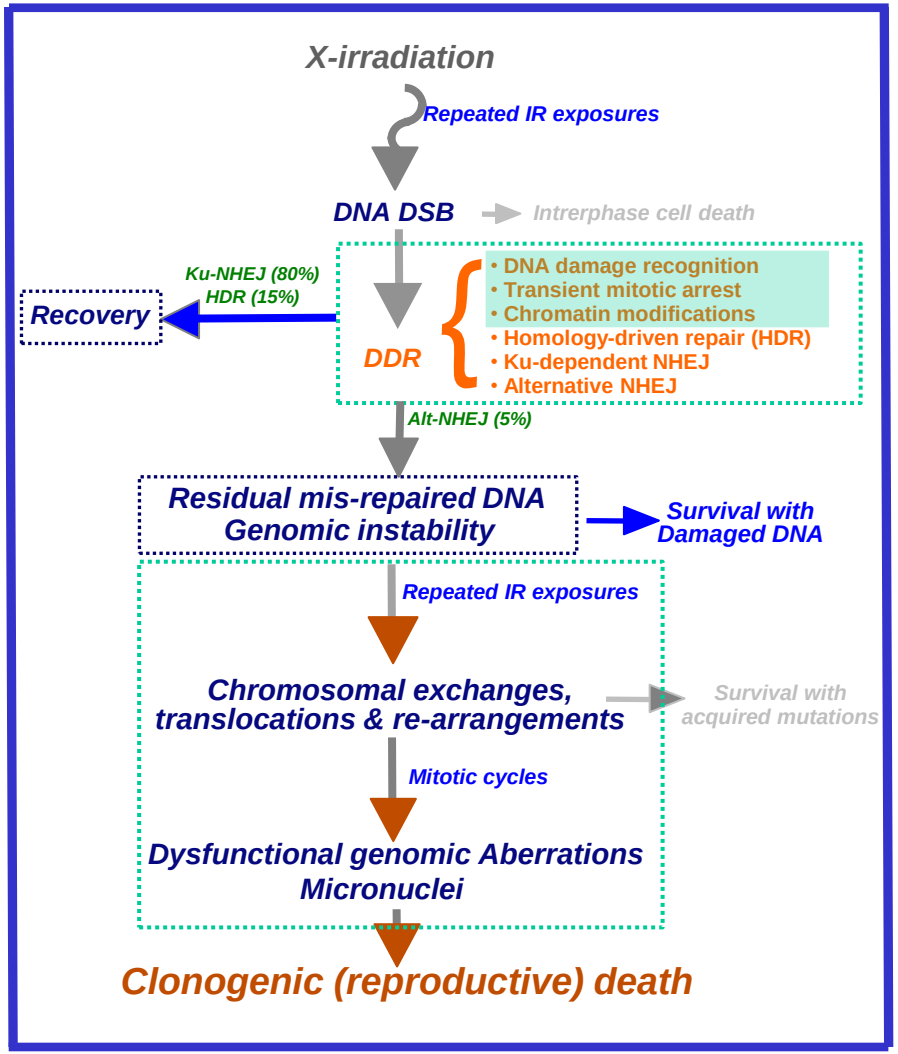
Radiosensitive cells repair poorly
Radioresistant cells repair proficiently



Cure of human tumors with Fractionated RT

	TCD_{50}	γ_{50}
Hodgkin's Disease	*21.4*	*1.62*
Anal canal	*47.0*	*0.78*
Lung	*51.3*	*1.61*
Breast	*59.4*	*1.18*
Nasopharynx	*61.6*	*3.38*
Larynx	*62.4*	*1.99*
Prostate	*65.6*	*2.0*
Hypopharynx	*70.4*	*1.21*

- The optimal fractionation scheme is 1.8-2.0Gy/d x 5/wk
- Each tumor has a specific dose-response phenotype
- There is rank ordering of tumor cure dose by tumor type
- Collateral normal tissue damage restricts tumor cure to 65%



The Basic Tenets of Tumor Cure By Radiation: The Single Target Model

Genomic instability promotes conversion of misrepaired DSB's into secondary genomic aberrations. Therefore,

mitosis-dependent
linear-quadratic relationship with dose (LQ model may be used to predict effect)
lethal lesions after single low dose exposure insufficient for cure
phenotypic variations by tumor type

Biological Optimization of Local Tumor Cure: The Case For Single Dose Radiotherapy (SD-IGRT)

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High dose single fraction RT is extensively used in the clinical practice:

Brain radiosurgery

Extracranial SD-IGRT (SBRT)

Intra Operative Radiation Therapy (IORT)

Are we exploiting a different biology?

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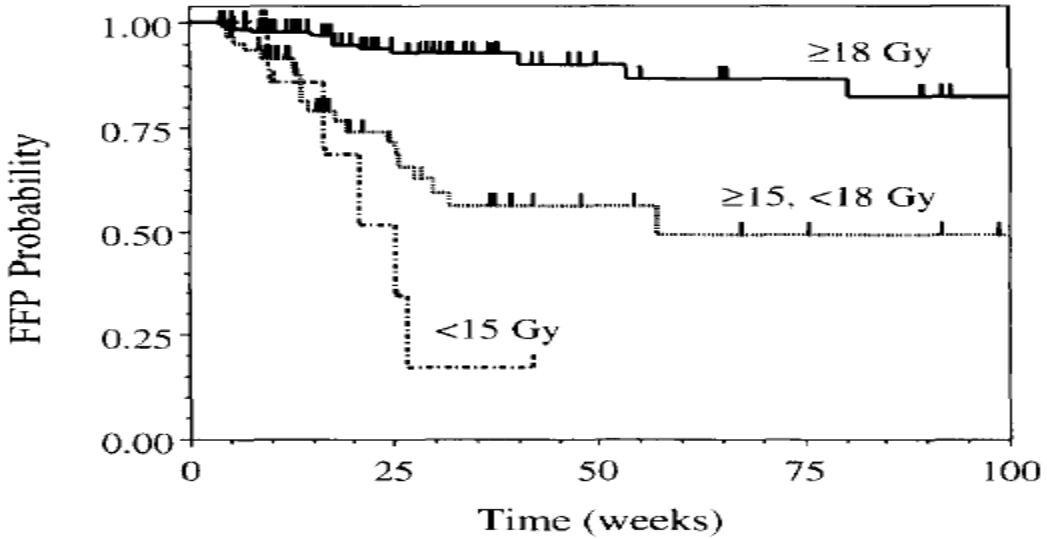
Stereotactic Single-Dose Radiotherapy For Brain Metastases*: Relationship of Dose and Local Control

UCSF Series; Shiah, IJROBP, 37,375, 1997



*261 lesions in 119 patients with lung, breast, melanoma, renal, colorectal, testicular, gynecological and thyroid tumors

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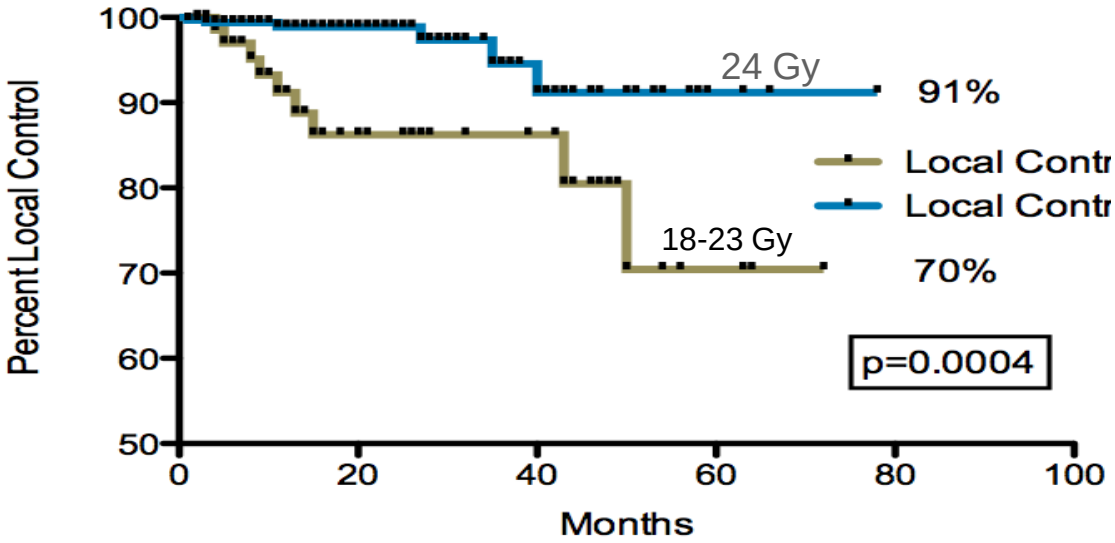
Single-Dose IGRT for Paraspinal Metastases

The MSKCC Series, Yamada et al IJROBP



- ***413 metastatic breast, colon, lung, prostate, renal, melanoma, sarcoma, and other primaries.***

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The SD tumour cure defies basic tenets of clinical radiobiology

- 24 Gy is a significantly lower dose for TCD90 than predicted from fractionated model formalisms (e.g. LQ)

- All tumor types, whether sensitive or resistant to fractionated RT, respond with ~90% local cure

- The difference in Single Dose *vs.* fractionated tumour phenotype responses suggests different mechanisms of action

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Therefore

A two-target model has been put forward in which tumour microvasculature undergoes dysfunction leading to stem cell apoptosis

(Fuks & Kolensky, 2003)

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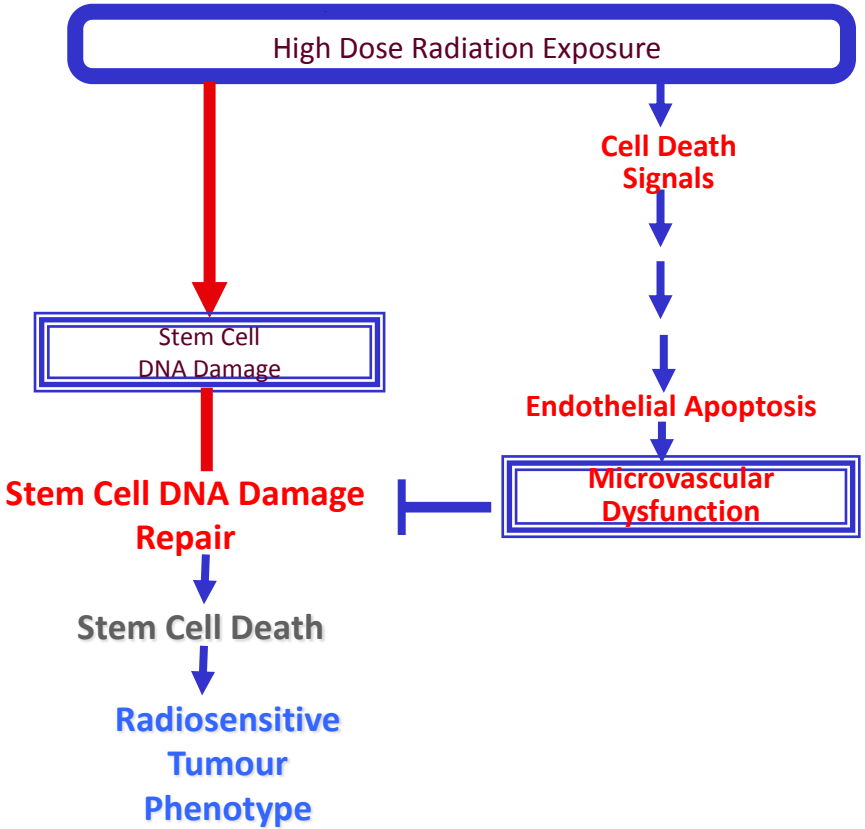
“The two target model”



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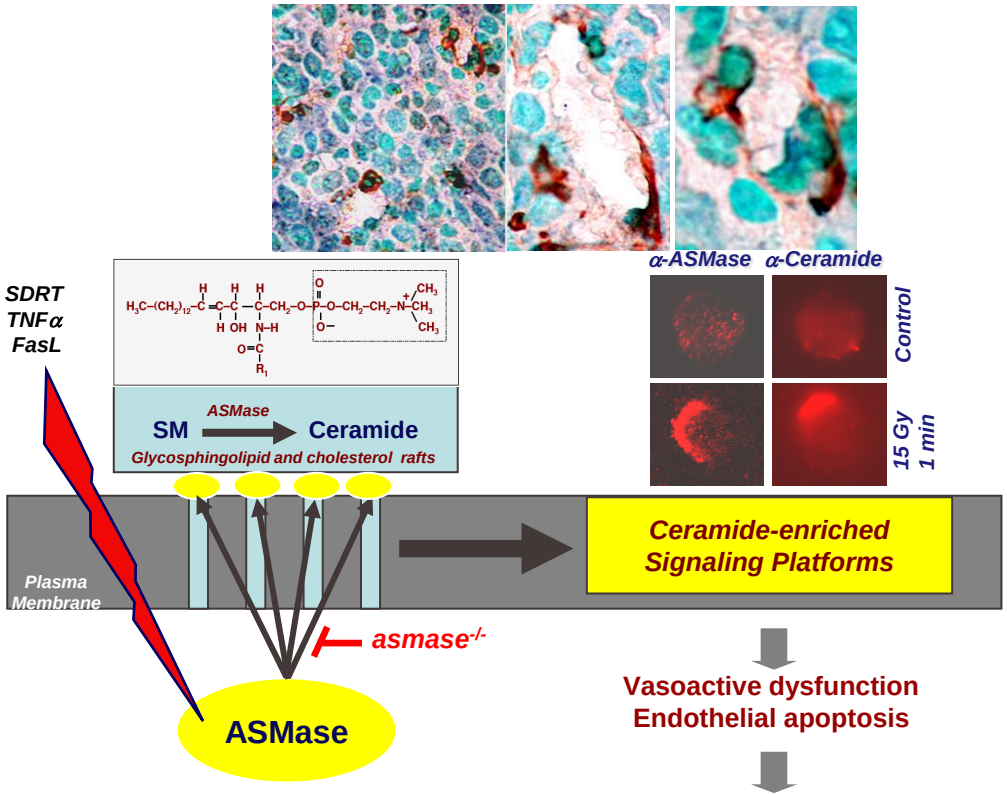
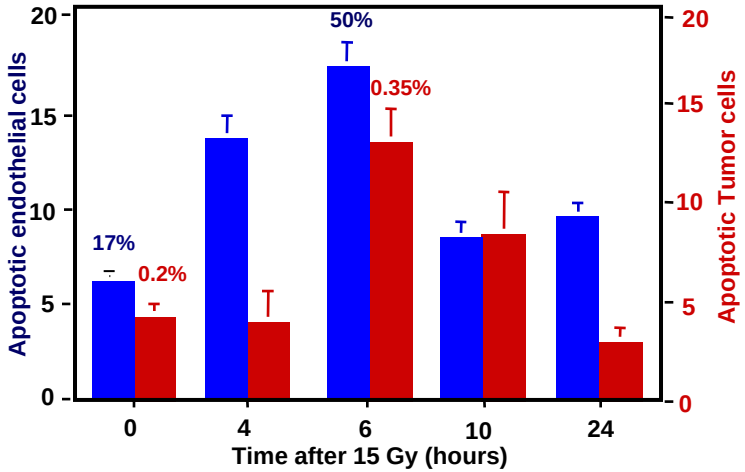
Acid sphingomyelinase (asmase) mediated vascular dysfunction

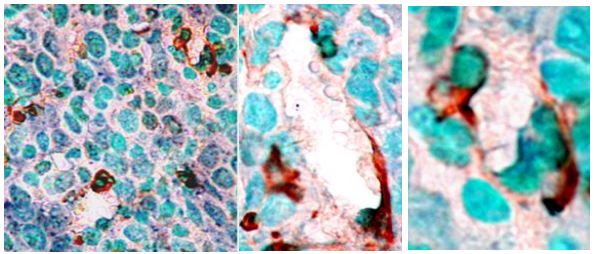
MCA/129 Fibrosarcoma; 4hr after 15 Gy

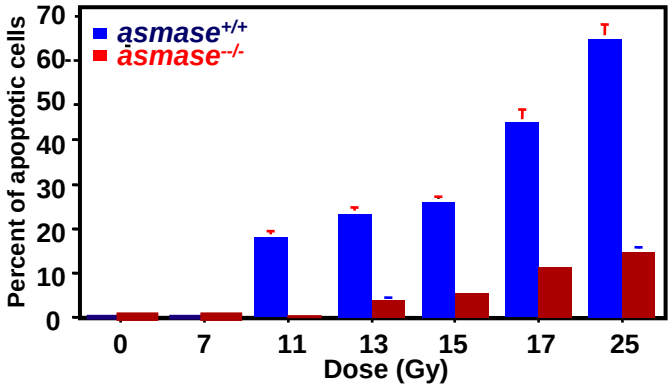




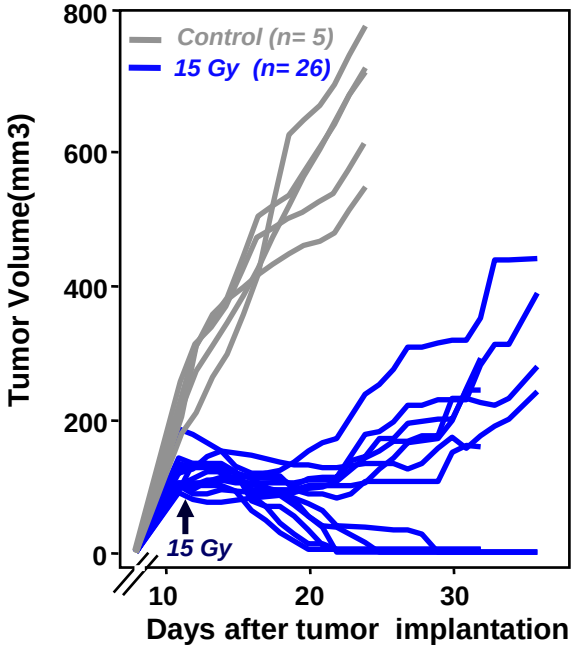
Acid sphingomyelinase (asmase) animal model
Knockout asmase -/-

MCA/129 Fibrosarcoma; 4hr after 15 Gy



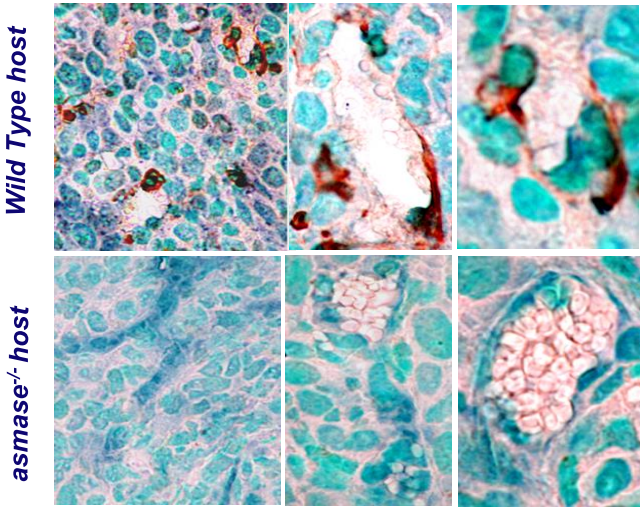


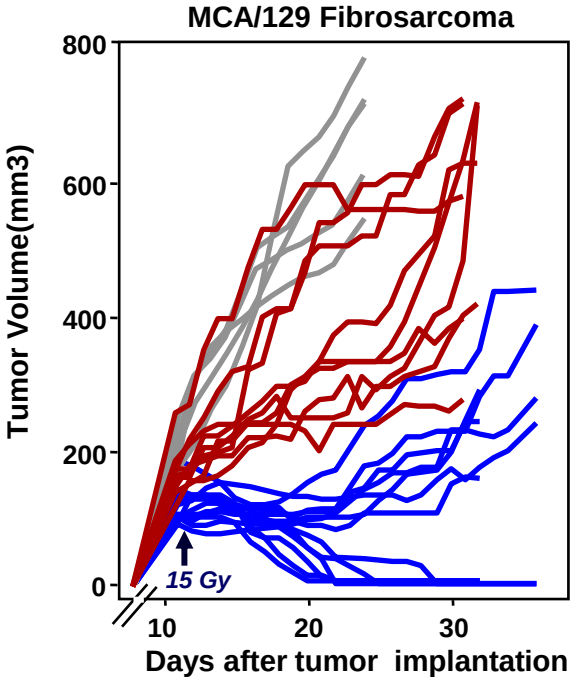
MCA/129 Fibrosarcoma



Garcia-Barros, Science, 2003

MCA/129 Fibrosarcoma; 4hr after 15 Gy



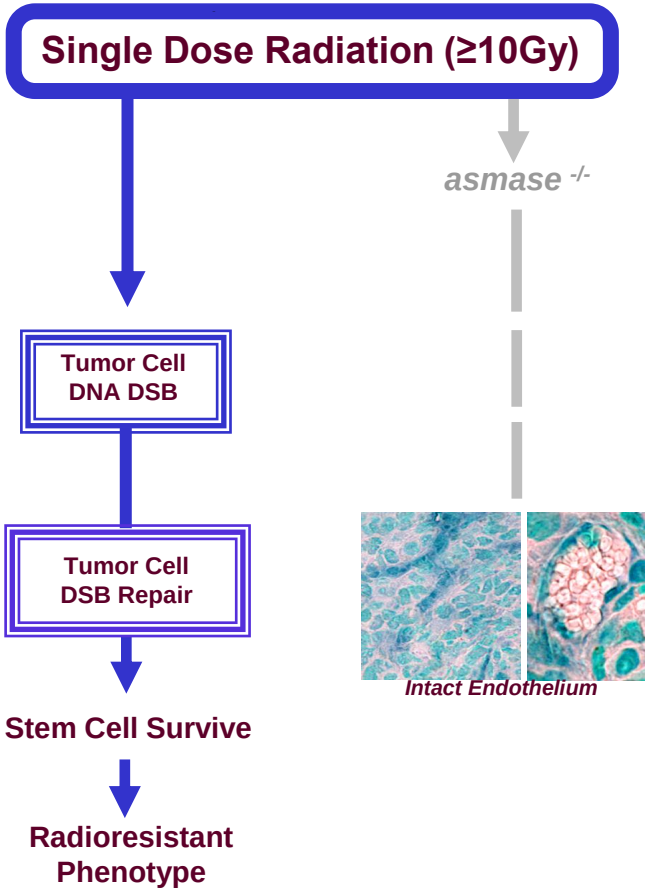


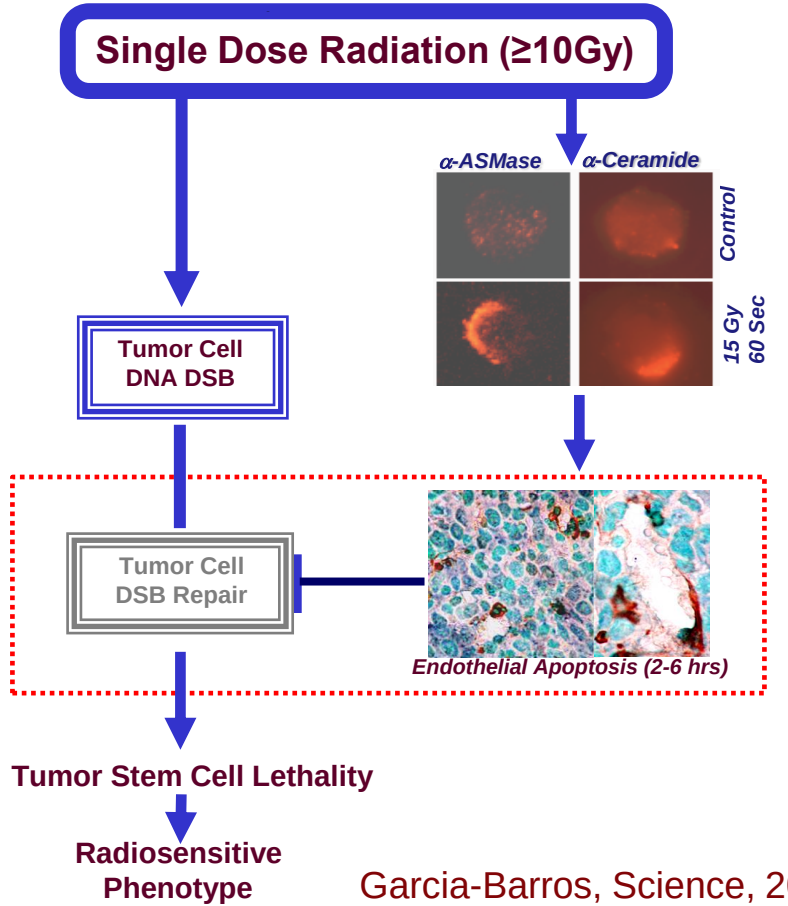
The radioresistant tumor phenotype in asmase$^{-/-}$ hosts implies microvascular damage and tumor cell lethality are linked

	asmase$^{+/+}$	asmase$^{-/-}$
CR at 30 Days	12/26 (46%)	0/15 (0%)***
TGD (Days)	13.3±2.9	6.7±2.8

Garcia-Barros, Science,300,1155,2003

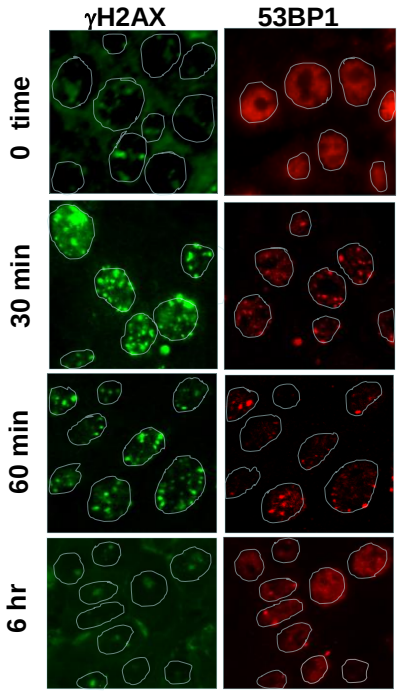
SD-RT operates a two-target model, defying the basic concept that the inherent DSB repair setting is the stand alone determinant of radiation treatment outcome

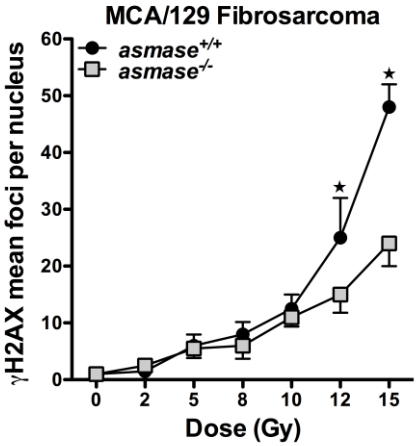


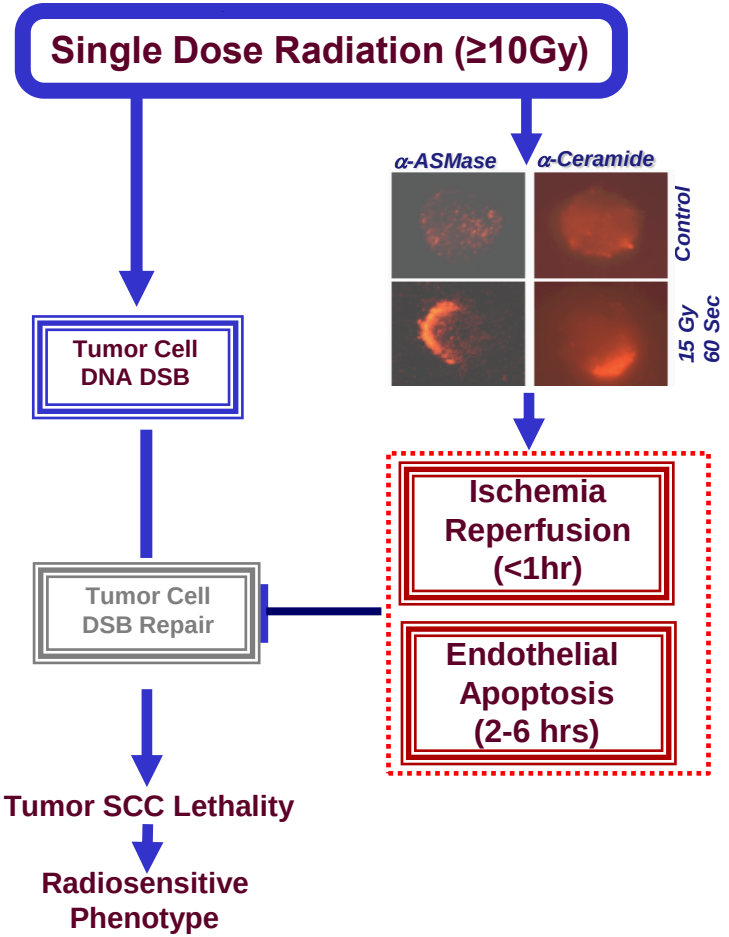


Garcia-Barros, Science, 2003

ASMase-mediated Microvascular Dysfunction Impairs DSB Repair (Dose Curves at 6 hrs)

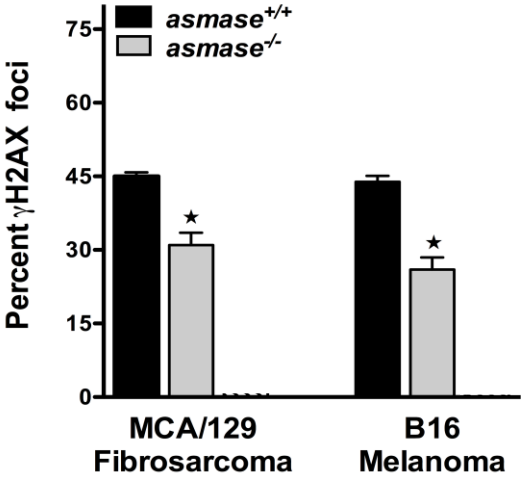


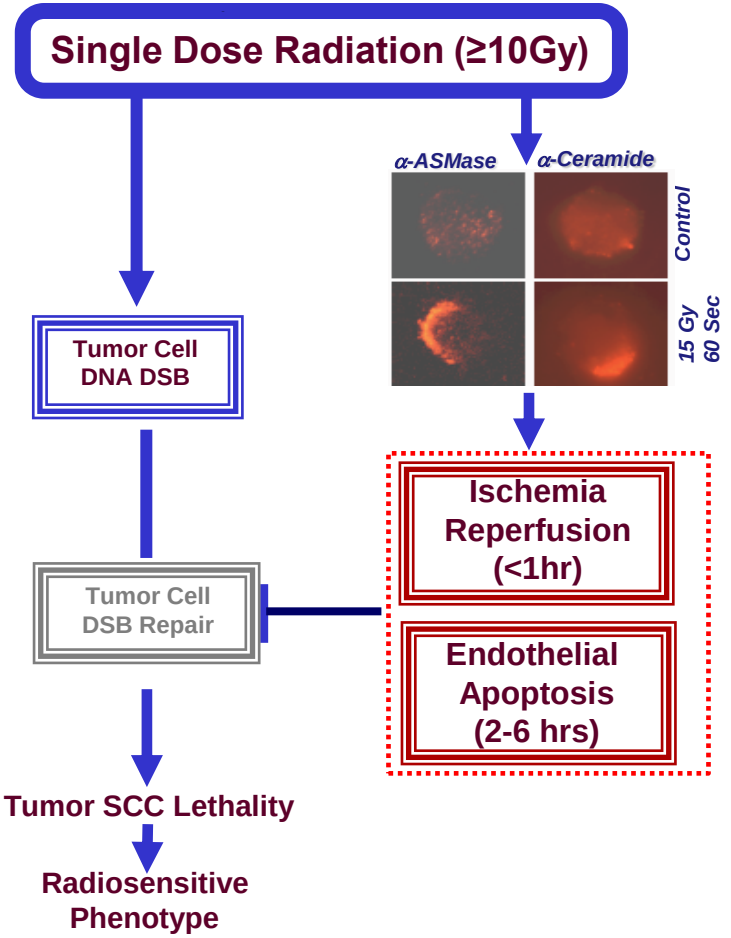




Microvascular Dysfunction Increases Residual DSB damage at 24 hrs After 15Gy

Tumor in asmase$^{-/-}$
2 min Clamping
immediately after
15 Gy and release





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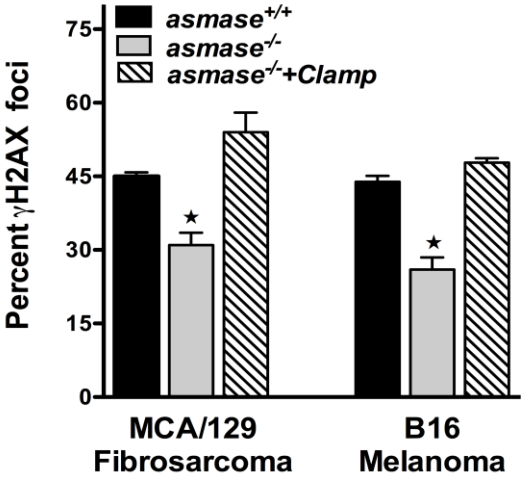
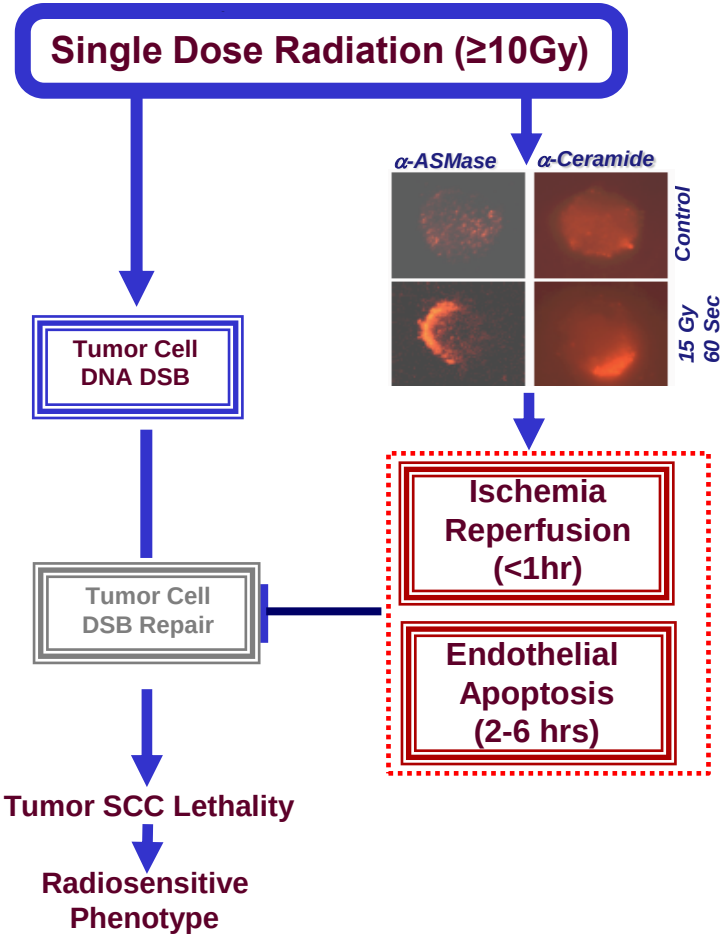
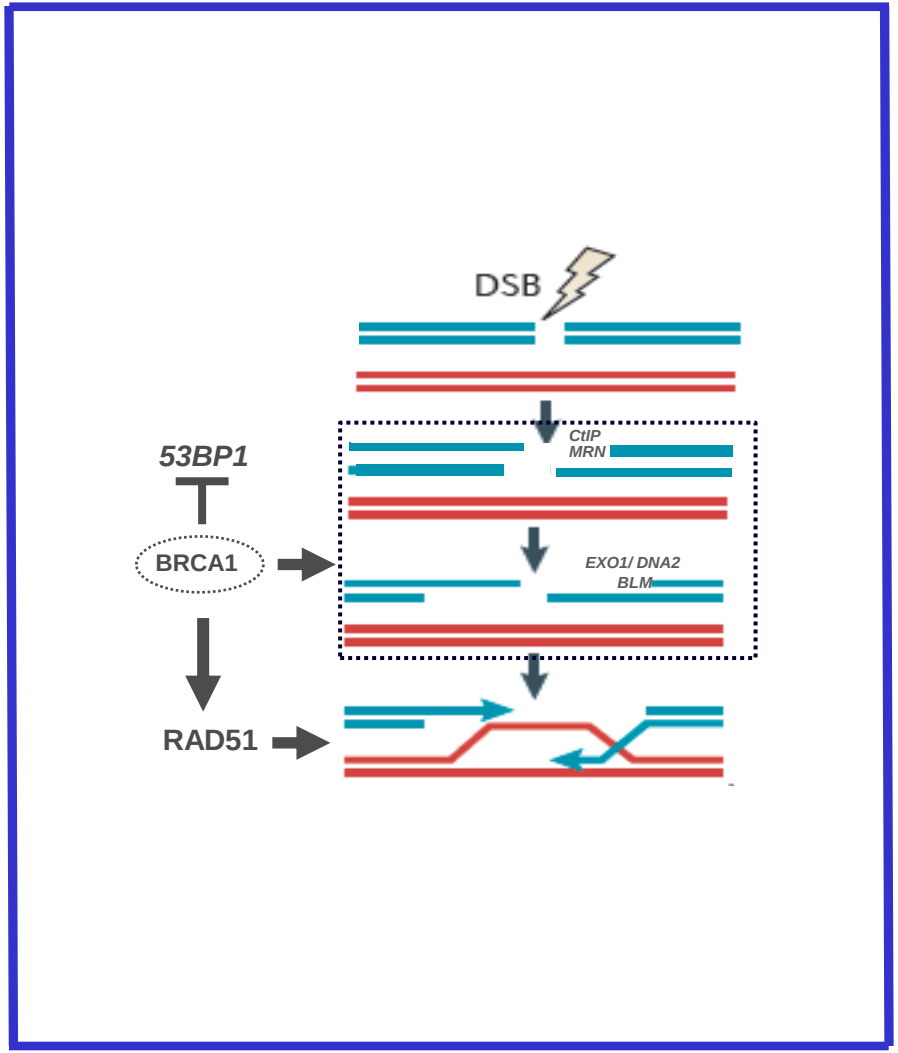


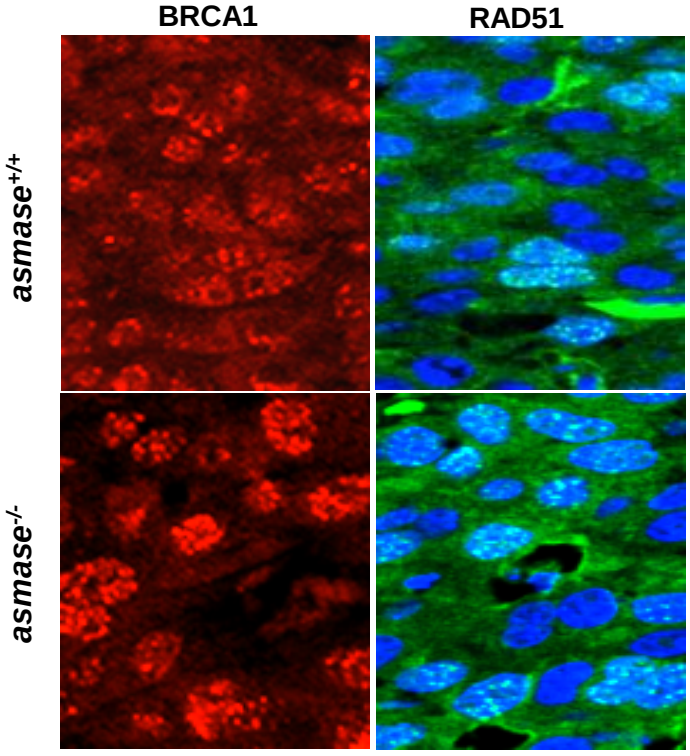


Homology-Directed Repair (HDR)

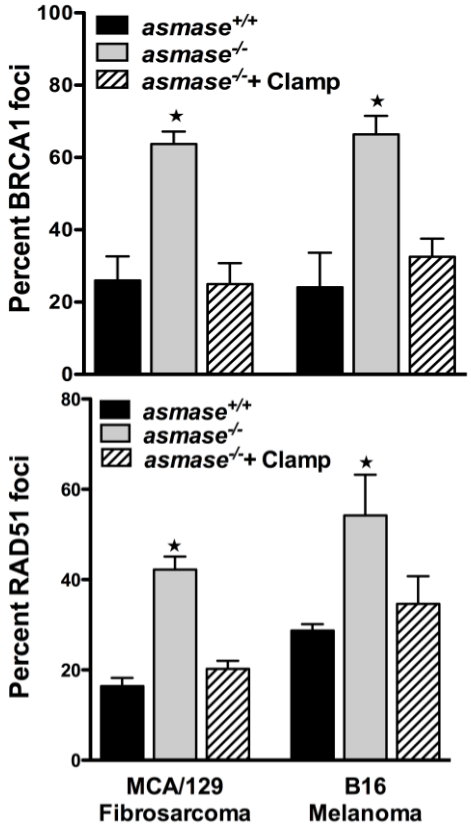
- High fidelity repair at S/G2 phase
- Sister chromatid serves as template for repair
- BRCA1 is the master regulator
  - regulates CtiP/MR in generating 3'ssDNA overhangs
  - regulates ssDNA resection by EXO1/DNA2BLM
  - engages RAD51 in HR
- BRCA1 is recruited via binding to the RAP80 complex



Ischemia/reperfusion represses BRCA1/RDA51 recruitment into repair foci inactivating HDR

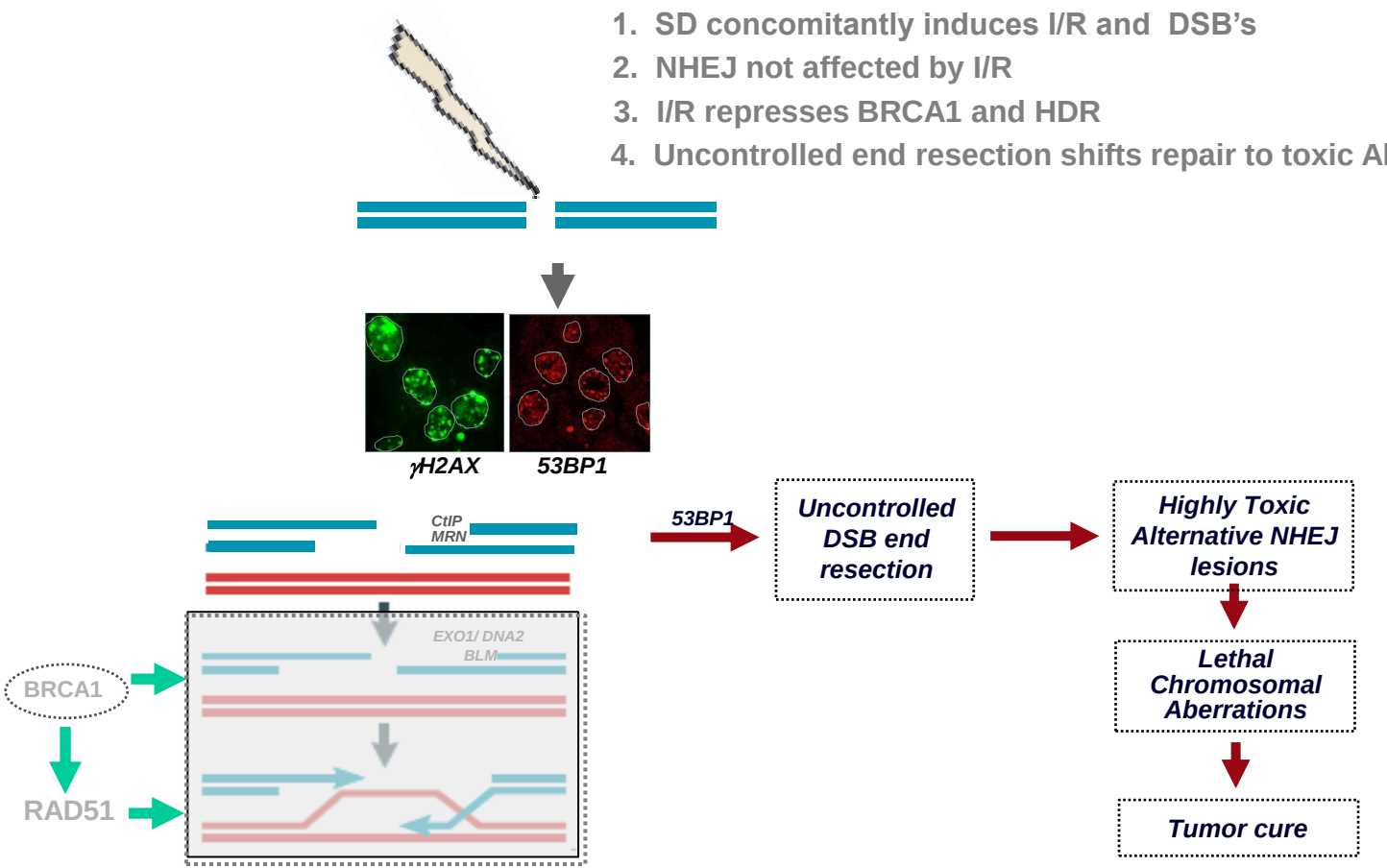


Recruitment of BRCA1 and RAD51 into IRIF occurs at 3-6 hrs after irradiation

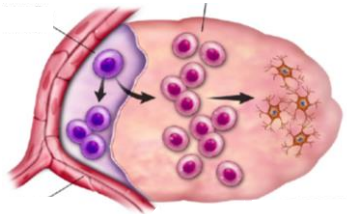


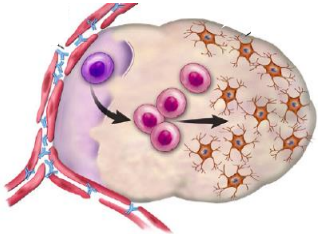
The pathophysiology of ischemia/reperfusion engagement in tumor cure by SDRT

1. SD concomitantly induces I/R and DSB's
2. NHEJ not affected by I/R
3. I/R represses BRCA1 and HDR
4. Uncontrolled end resection shifts repair to toxic Alt-NHEJ

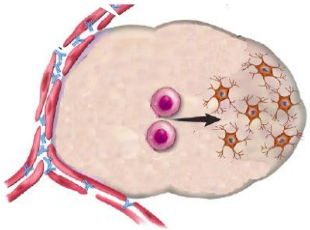


Single dose radiotherapy is effective in killing the stem cell





Tumor Growth Delay:
Tumor will relapse



Tumor Cure

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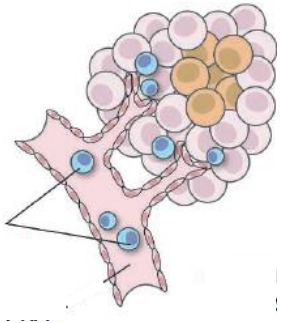
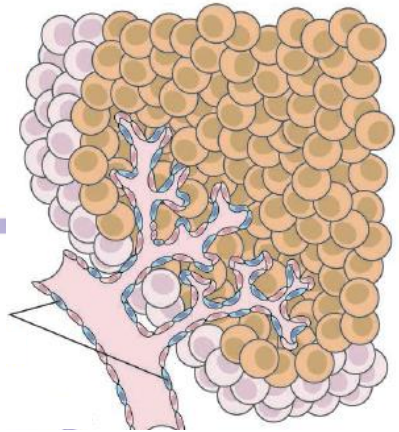
Exploiting (this) New Radiobiology



DRUG SENSITIVE MICROSCOPIC TUMOR

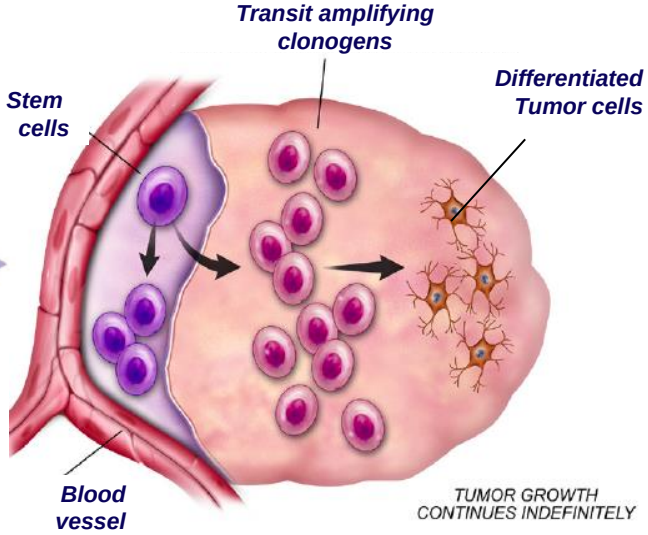
CHEMOTHERAPY

Drug sensitivity Switch



DRUG RESISTANT SUB-CLINICAL TUMOR

Tumor >1 cm³



MACROSCOPIC TUMOR

SDRT

- ***A paradigm shift:*** **Engagement of endothelial dysfunction, not just tumor stem cell DNA damage, required for SDRT cure**

- ***The new biology:*** **A co-dependent two-target model with ischemia / reperfusion re-programing DDR to engage aberrant DSB repair**

- ***The biochemistry:*** **SUMO enzymes oxidation by post-reperfusion ROS impairs RAP80/BRCA1/RPA/RAD51 recruitment into repair foci**

- ***The pathophysiology:*** **Epigenetic loss-of-function BRCA1/HDR coupled with functional 53BP1 diverts DSB repair to an aberrant Alt-NHEJ pathway**

- ***A new concept:*** **Intensity of the ASMase-mediated I/R, not the number of DSBs produced, is the critical determinant of SDRT lethality, demonstrated by sensitivity of TCD90 to modulation of ASMase activity**

` ***The ASMase rheostat***

Single Dose Radiotherapy (SDRT): Is it different?

- ***Yes, it is new and is different conceptually dictating different strategic approach to treatment indications and design***
- ***biologically it is distinct from hypo-fractionated SBRT, the latter being subject to I/R conditioning***
- ***Provides the current most effective tumor ablation challenging surgery as a primary mode of human cancer cure***
- ***Demands new standards of diligence and QA; violation results in punitive regrets***

- The clinical vision: SD emerges as a highly effective, non-invasive mode of tumor ablation, potentially challenging surgery as primary mode of human cancer cure

Fractionated Radiotherapy

SDRT

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