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OMICS International has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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ZHONGNAN HOSPITAL OF WUHAN UNIVERSITY
Wuhan University

Mitochondria retrograde signaling regulates the radiosensitivity of NSCLC through NFkB /PI3K/AKT2/mTOR pathway

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April 27,2015

Outline

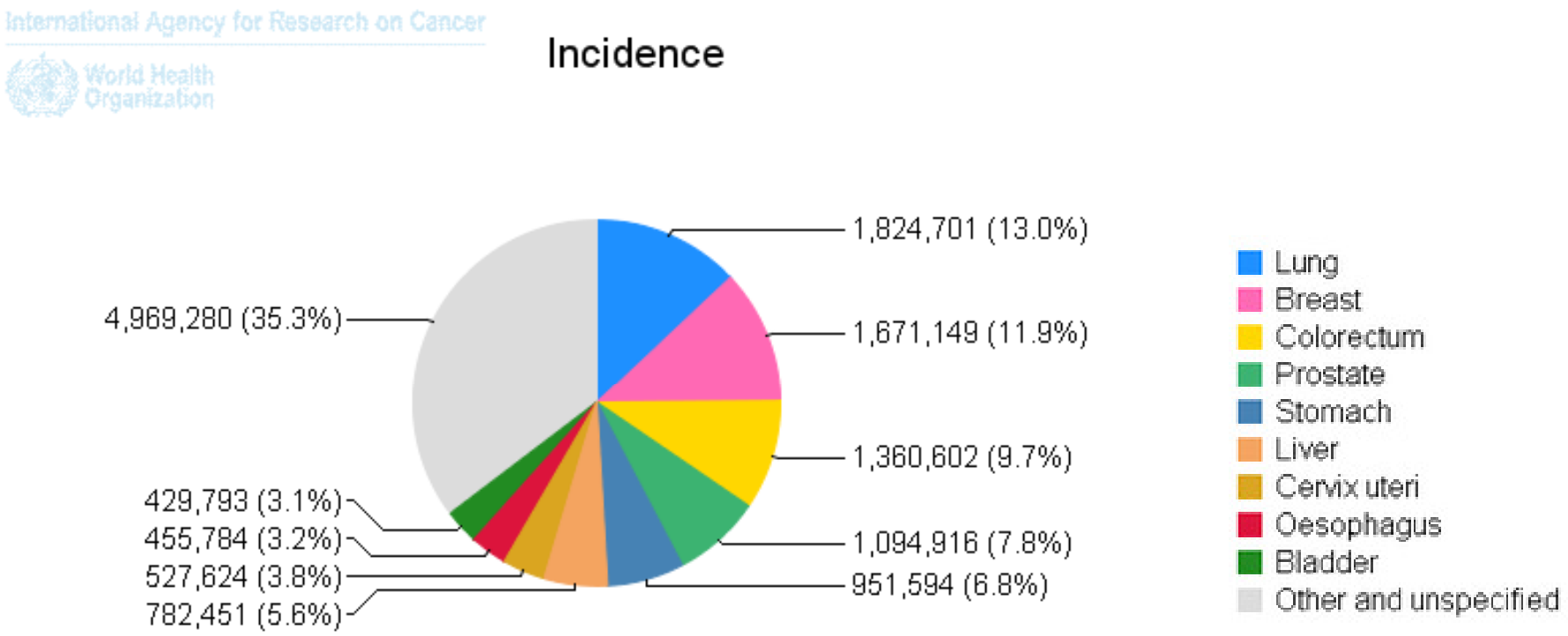
1. Introduction

2. mtDNA depletion and radiosensitivity in H1299 NSCLC cell line

3. Mitochondrial retrograde pathway related with radiosensitivity

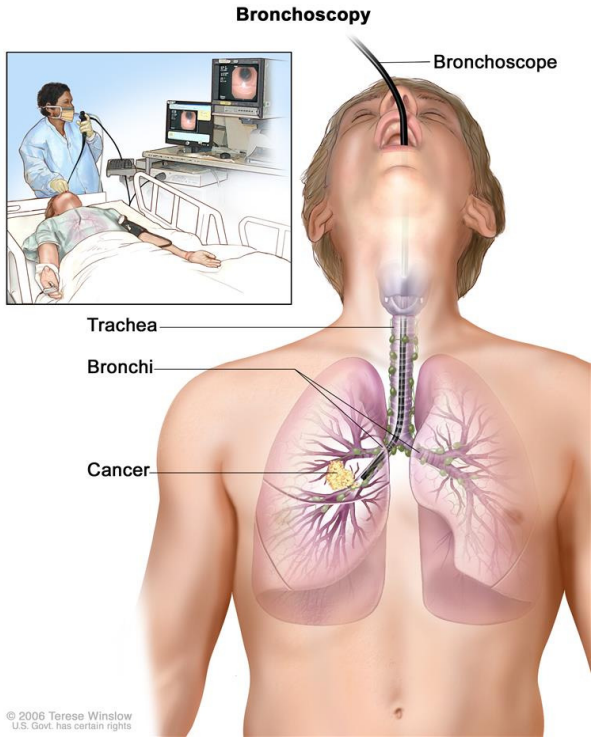
4. Summary

Introduction



GLOBOCAN: Estimated Cancer Incidence Worldwide in 2012.

(1) The main treatment options for NSCLC



Surgery

Radiofrequency ablation (RFA)

Radiation therapy

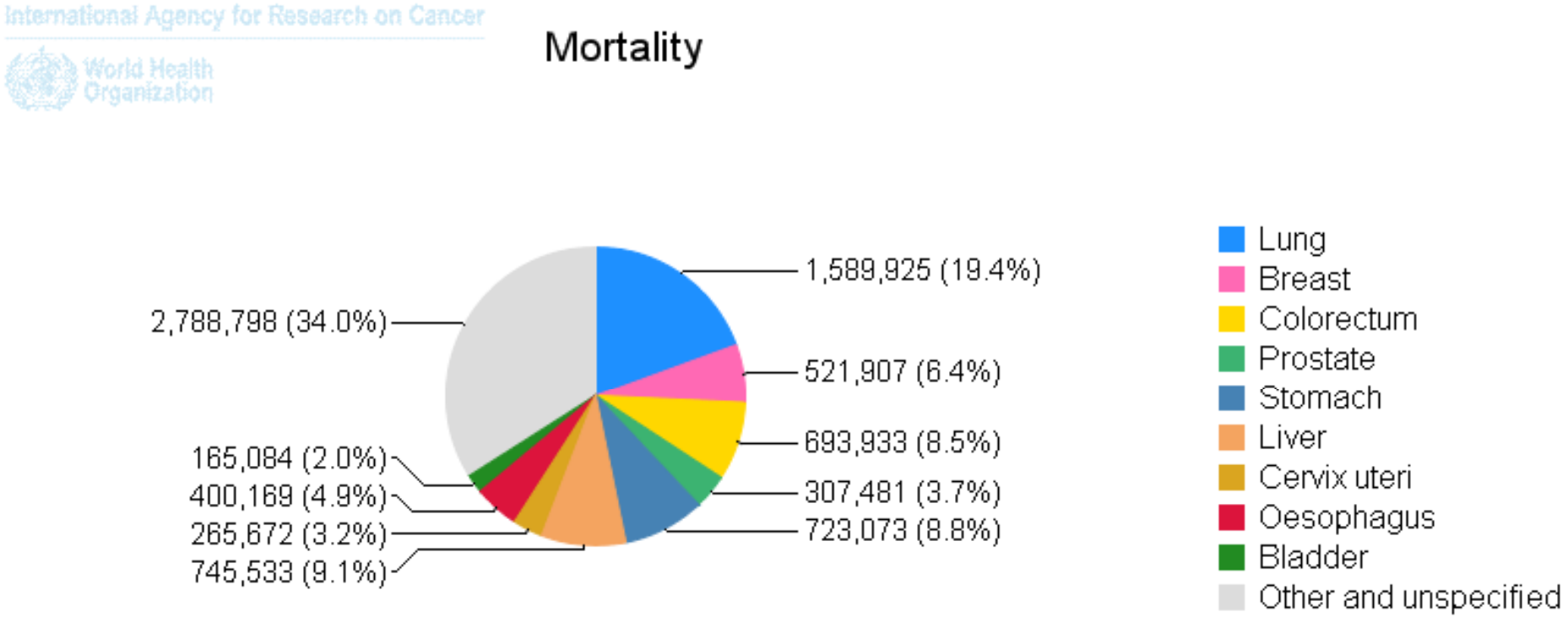
Chemotherapy

Targeted therapies

Immunotherapy

http://www.cancer.org/

(2) Mortality of NSCLC



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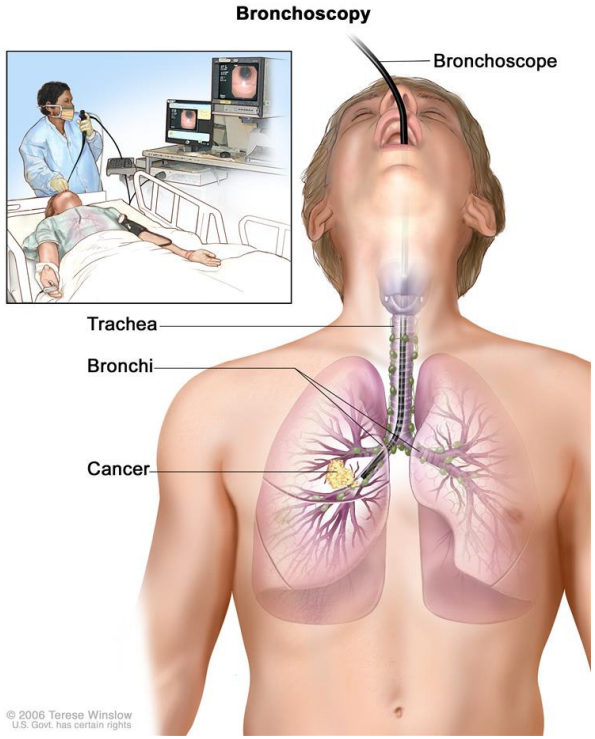


Surgery

Radiofrequency ablation (RFA)

Radiation therapy → **Radiosensitivity**

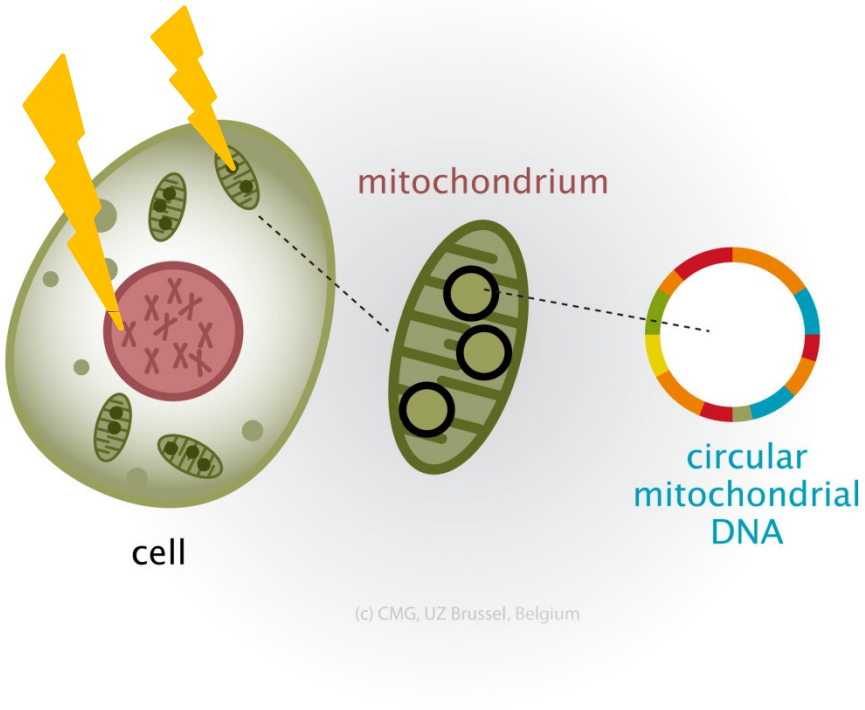
Chemotherapy

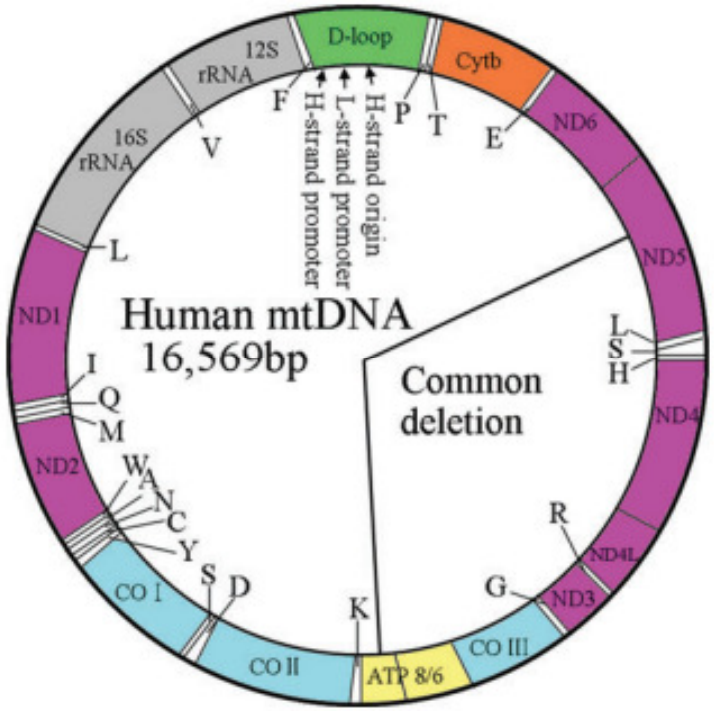
Targeted therapies

Immunotherapy

http://www.cancer.org/

(4) Mitochondria DNA and Radiosensitivity





- **constant exposure to mutagenic oxygen radicals**
- **lacks the protective mechanisms of DNA repair**

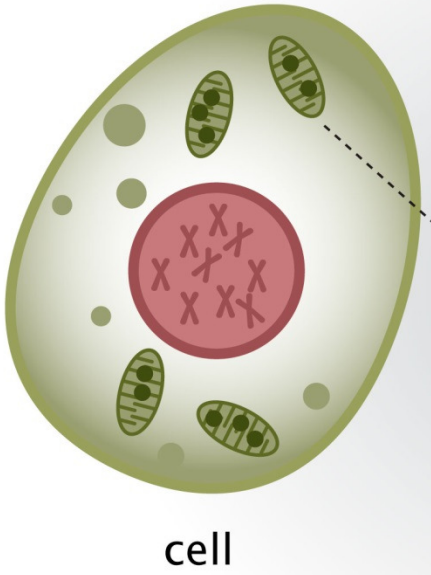
Roberts ER, Thomas KJ. Comput Struct Biotechnol J. 2013

(4) Mitochondria DNA and Radiosensitivity

Radiosensitivity

HeLa

wtp53



Radiosensitivity

Mia PaCa-2

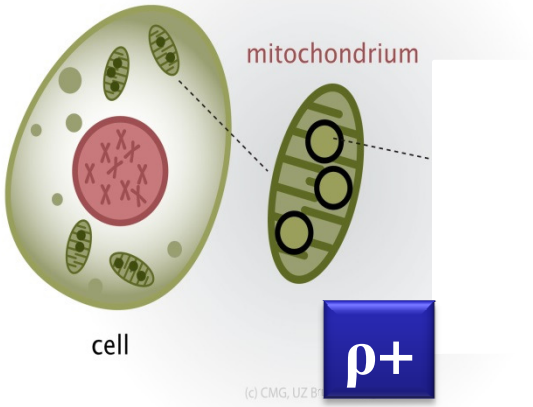
mtp53

J Biol Chem, 2005, 280:(44): 37169-37177

J Health Sci, 2005, 51:(3): 385-393.

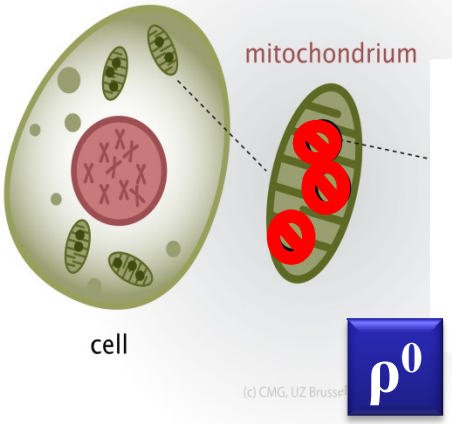
Roberts ER, Thomas KJ. Comput Struct Biotechnol J. 2013

(5) Alteration of Nuclear Gene Expression in ρ^0 Cells



Saccharomyces cerevisiae

microarray analysis



several nuclear genes ↑

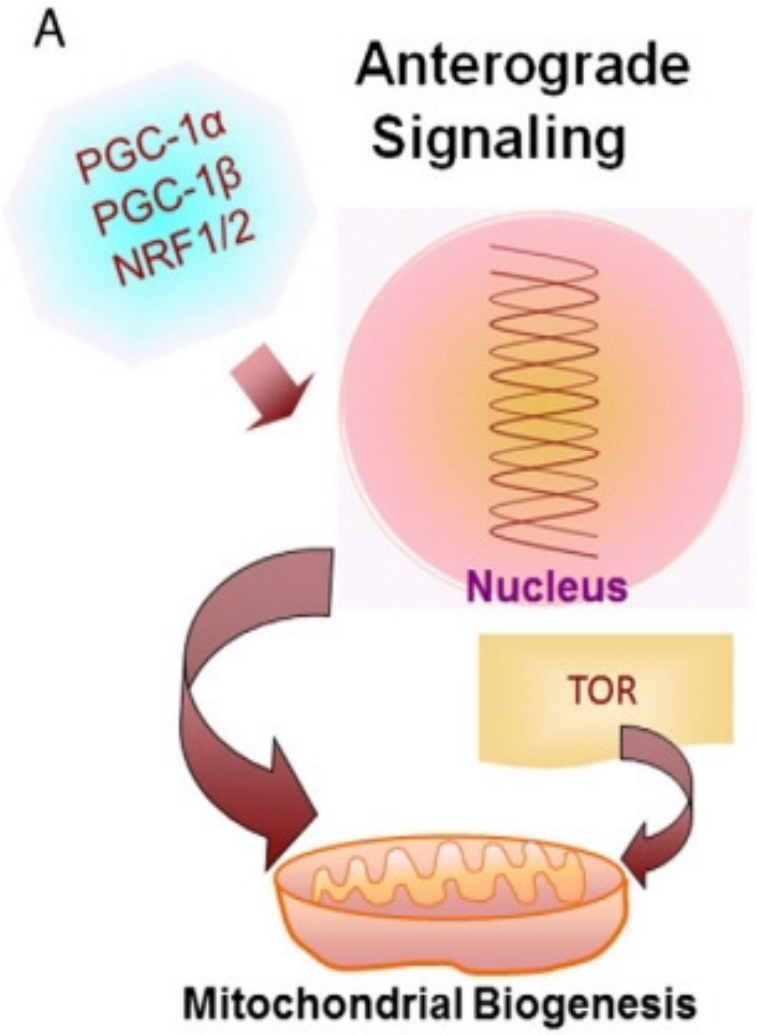
CIT2 **(citrate synthase)**

MRP13 **(mitochondrial ribosomal protein)**

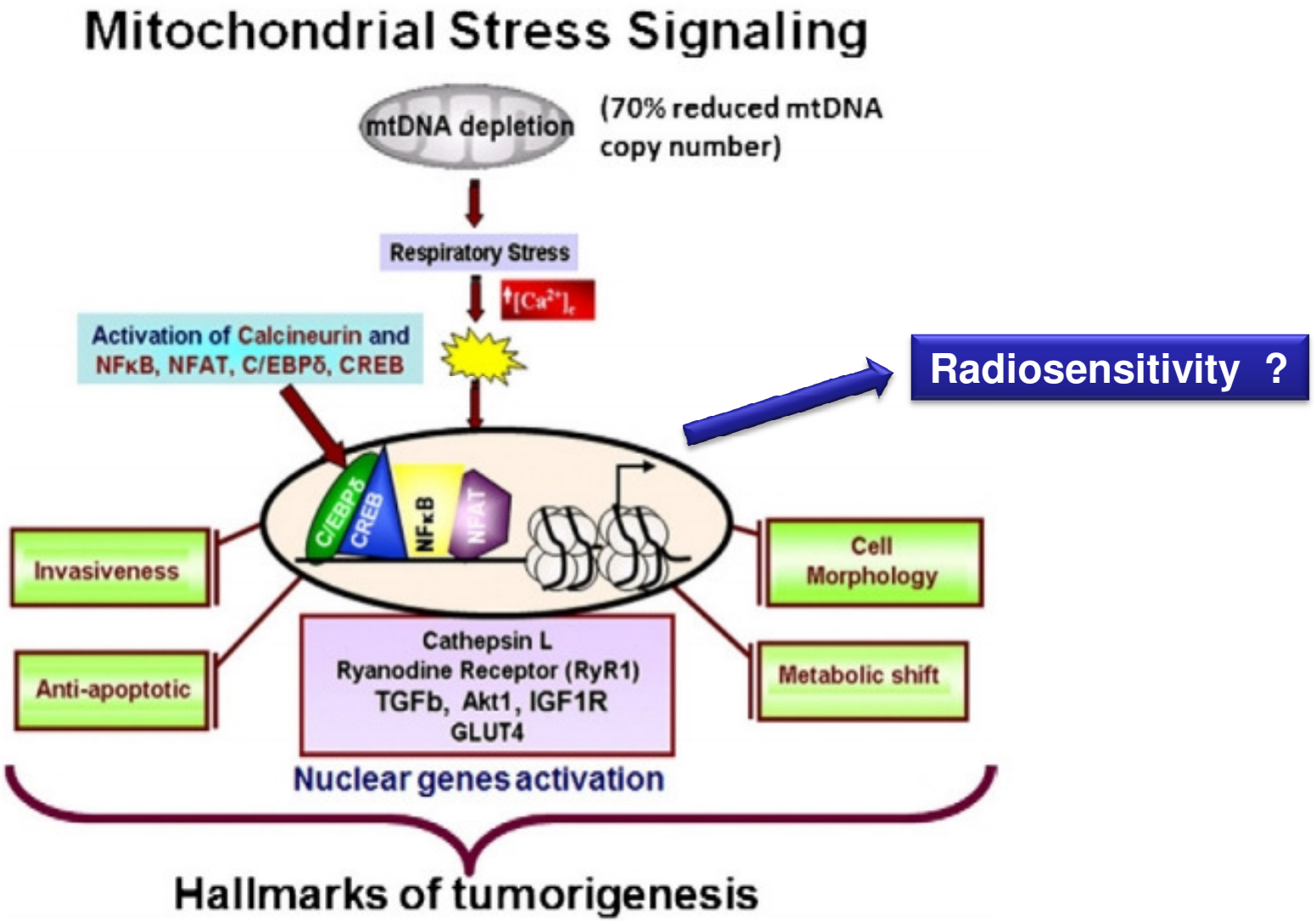
DLD3 **(D-lactate dehydrogenase)**

J Biol Chem, 2001, 276:(6): 4020-4027

(6) Communication between mitochondria and nucleus



(7) Mitochondria retrograde signaling，RTG



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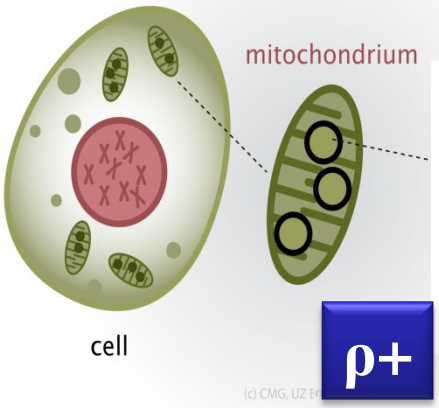
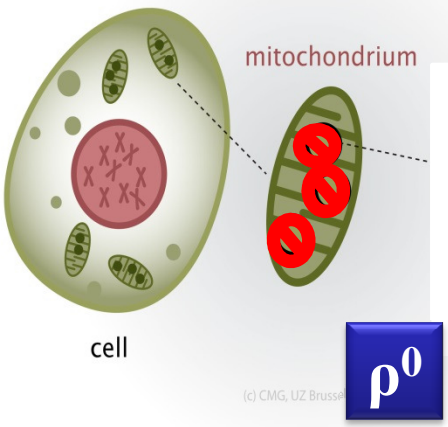
(1) Establishment of H1299 ρ^0 cell line



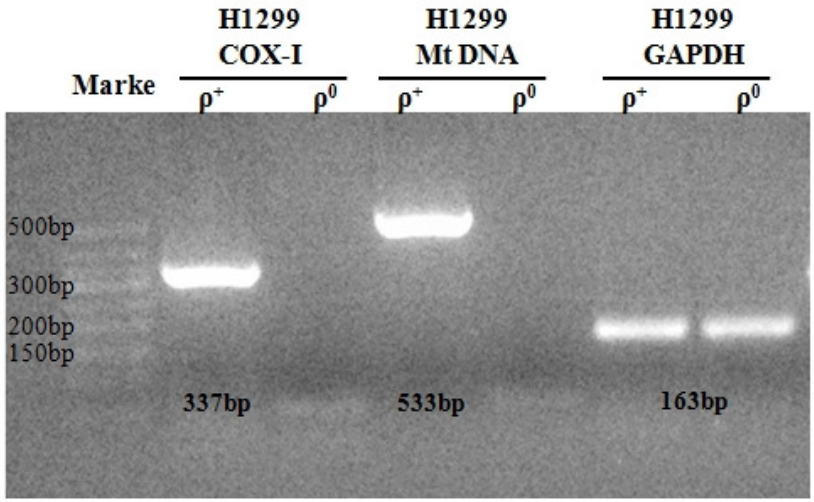
ethidium bromide(50ng/ml)

100ug/ml pyruvate

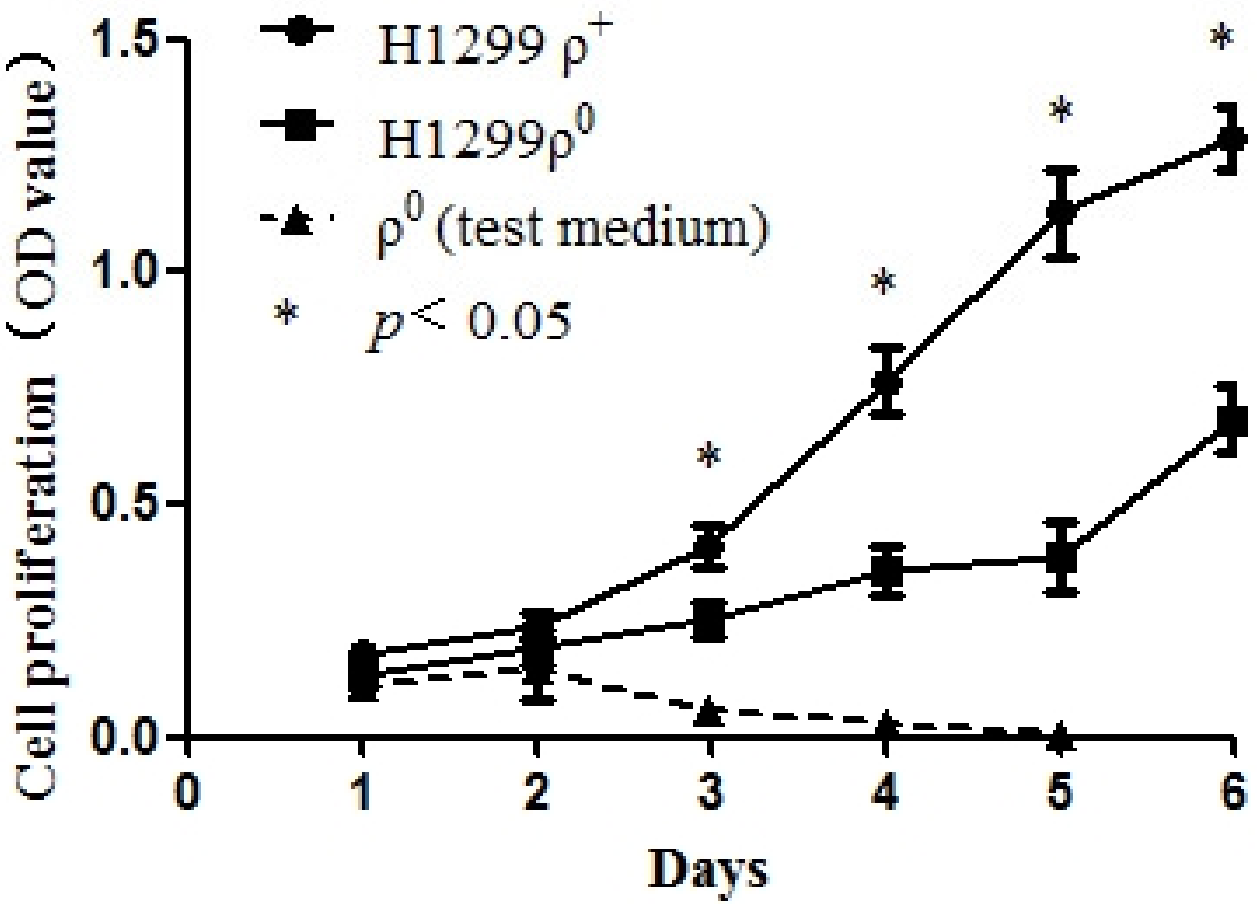
50ug/ml uridine



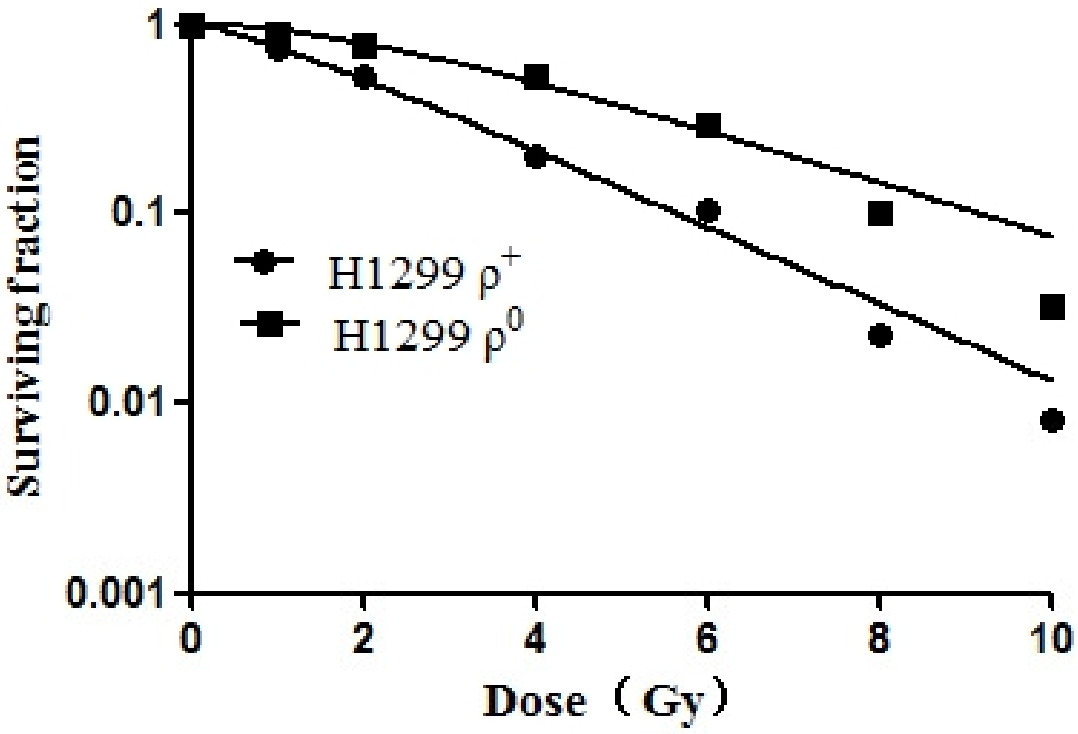
H1299 cell



(2) Cell growth defects identification



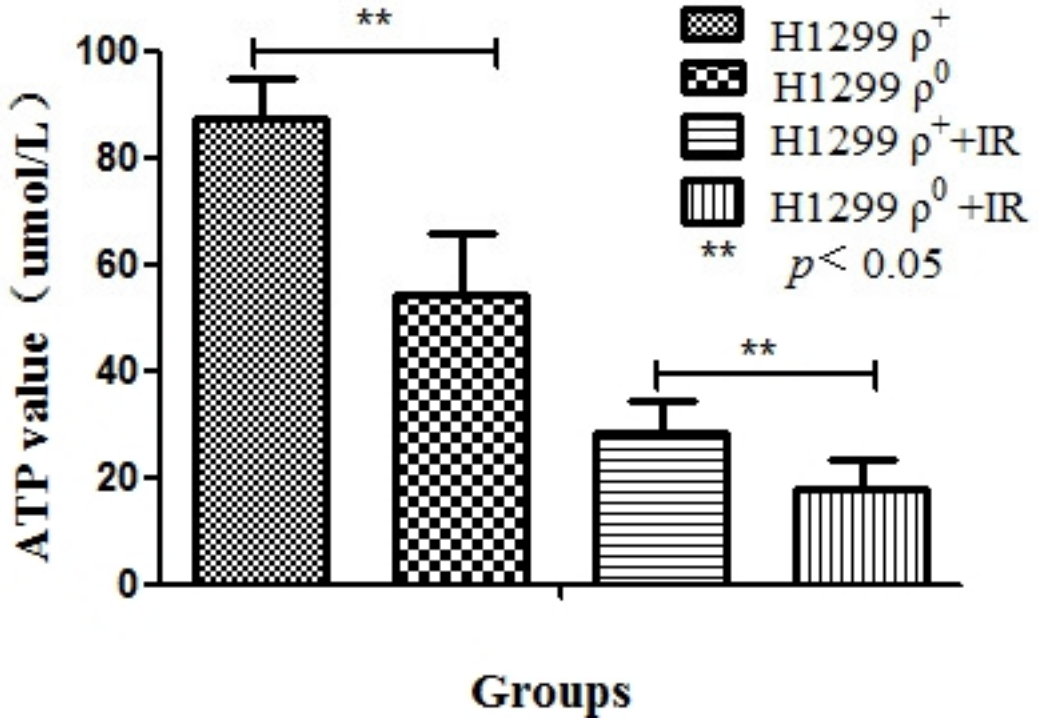
(3) Radiation response following irradiation



Cell lines	D_0	D_q	SF_2
H1299ρ⁰	2.993±0.028*	3.601±0.015*	0.788±0.058*
H1299ρ⁺	2.119±0.012*	0.983±0.033*	0.525±0.072*

H1299ρ⁰ cells are more radio resistant than H1299ρ⁺ cells

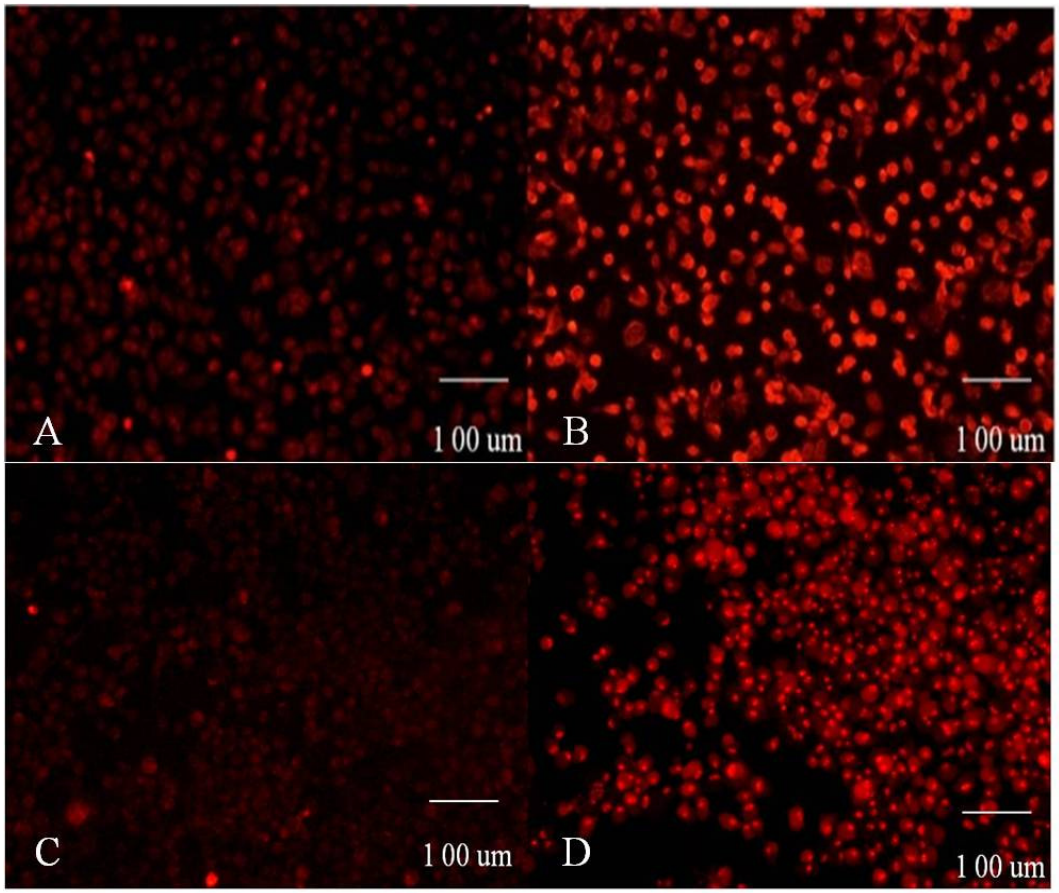
(4) ATP Assay

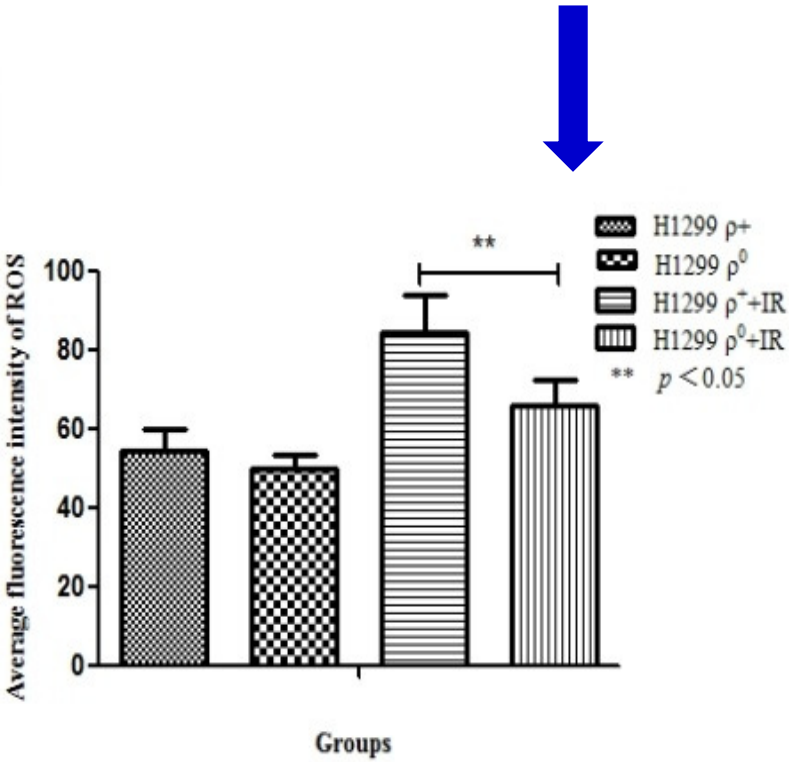


H1299ρ⁰ cells generated less ATP than H1299ρ⁺ cells

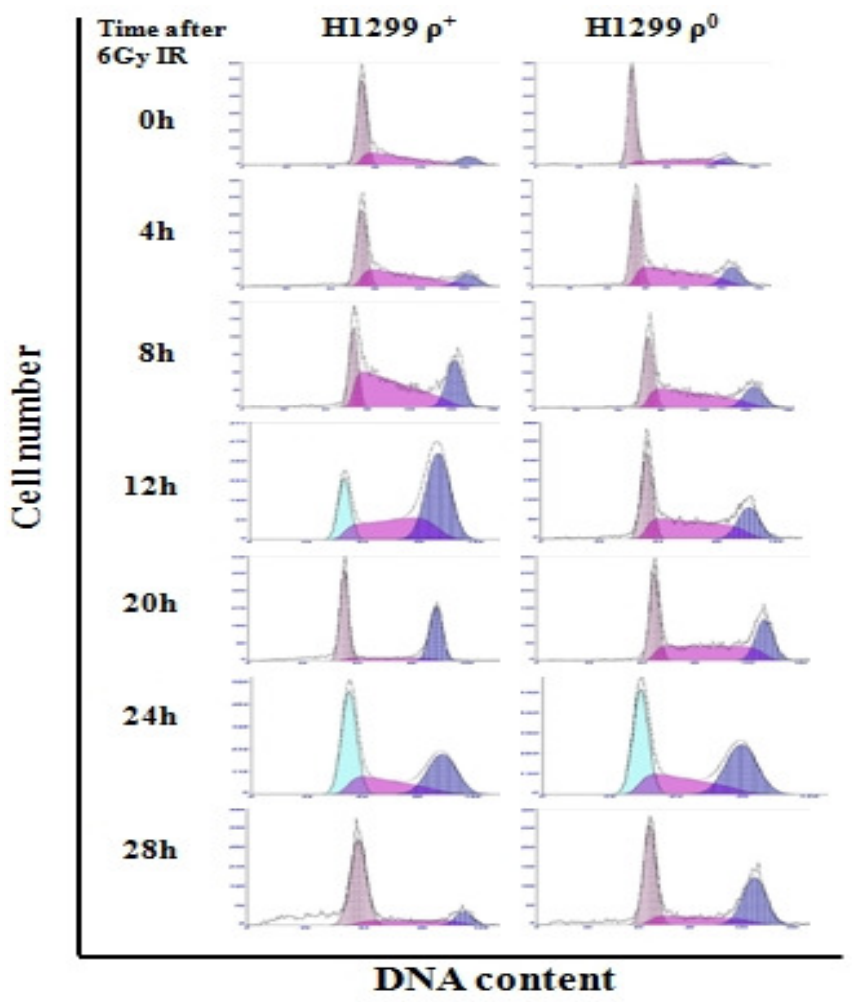
(5) ROS Assay

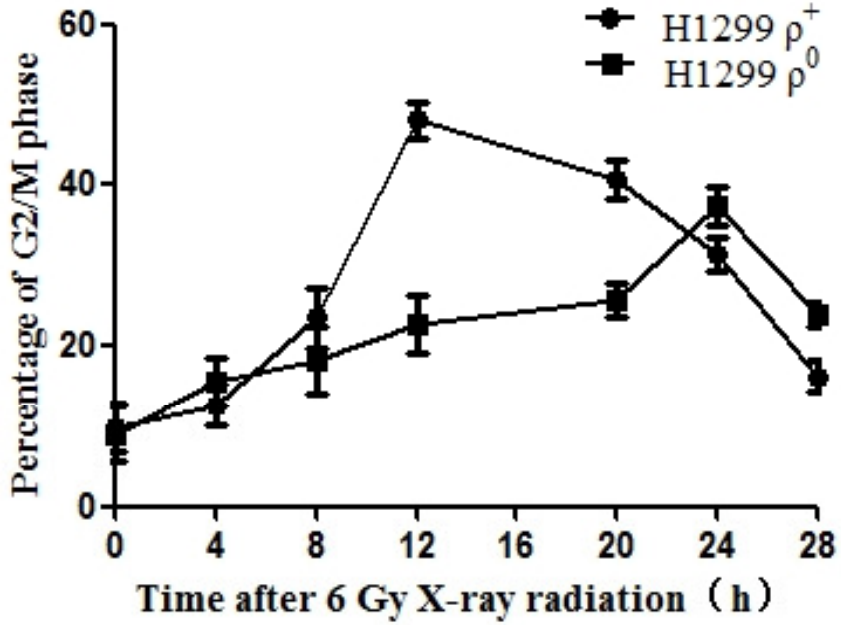
4Gy **-** **+**





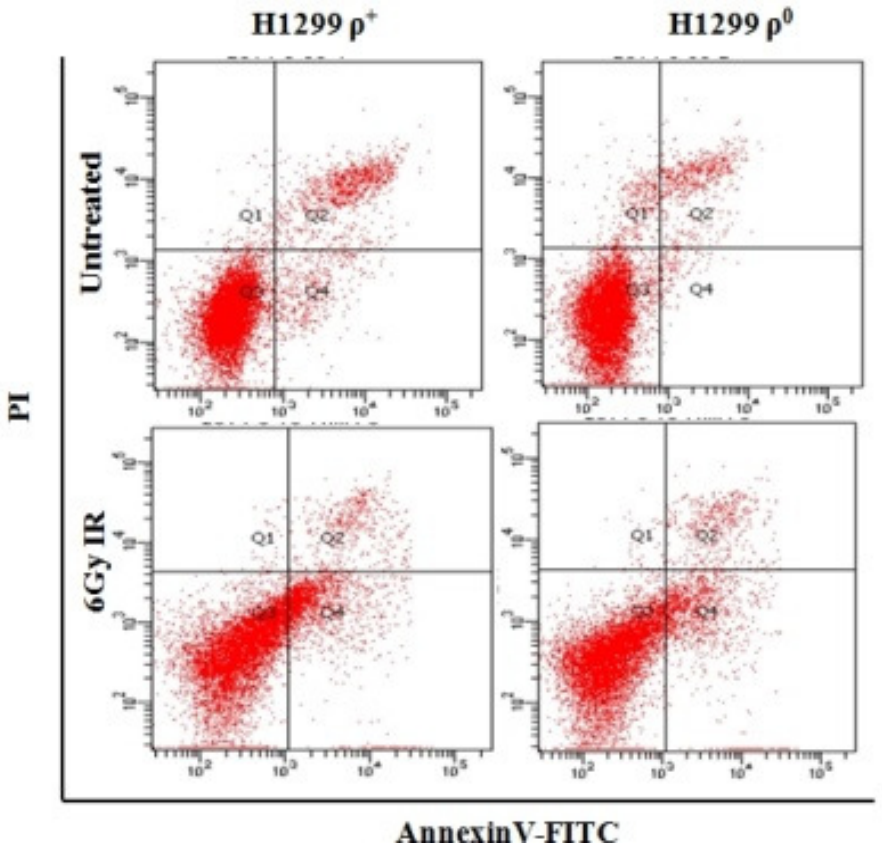
(6) Cell cycle change after 6Gy irradiation

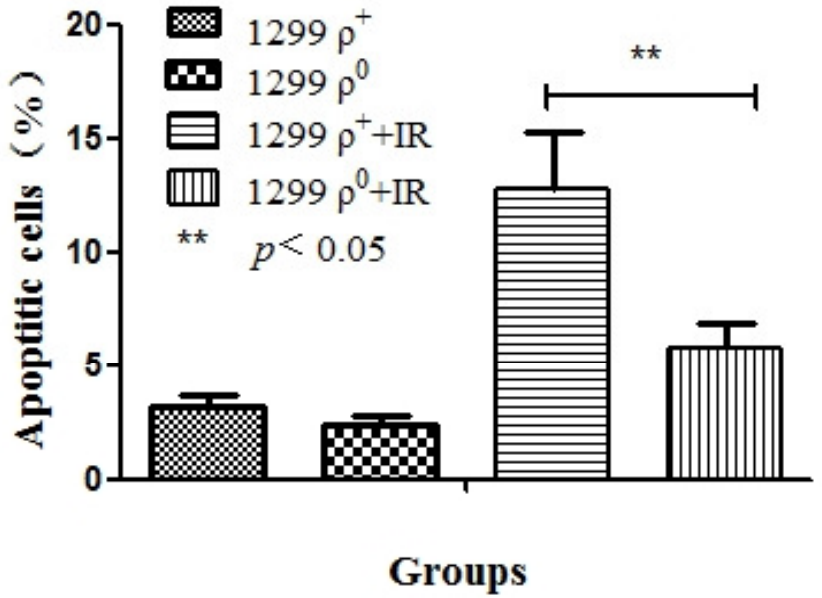




Exposure to ionizing radiation (6Gy) induced pronounced G2/M arrest in ρ0 cells

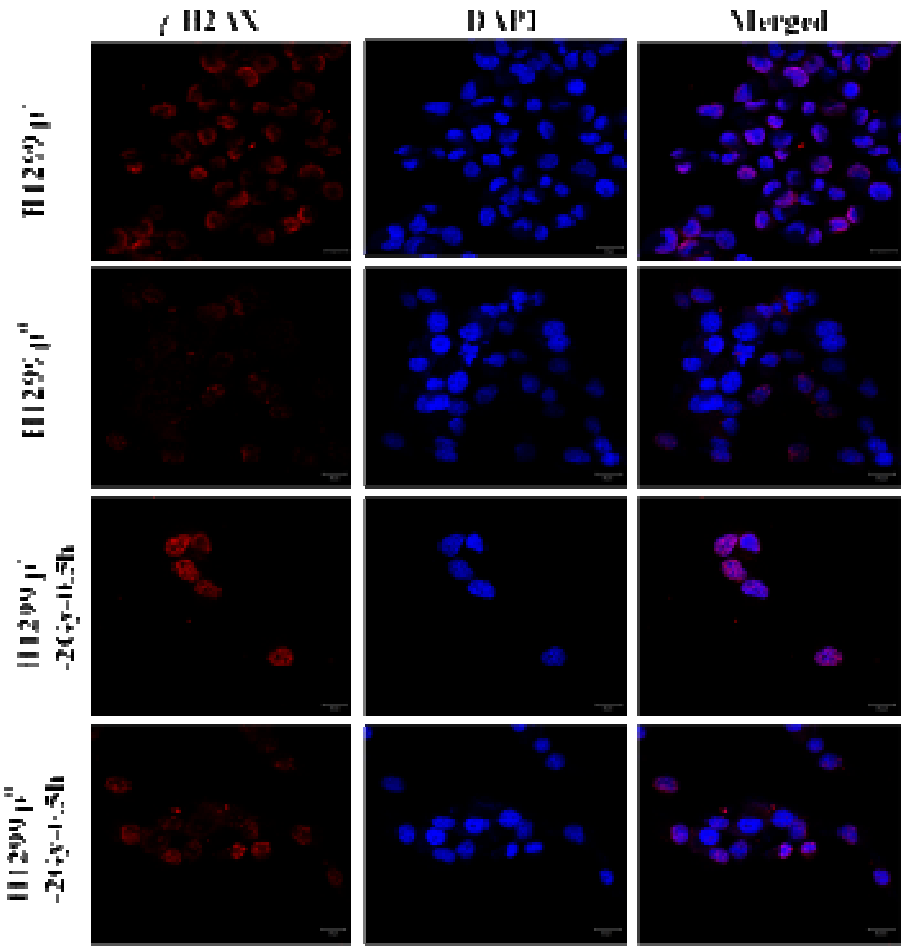
(7) Cell apoptosis after 6Gy irradiation

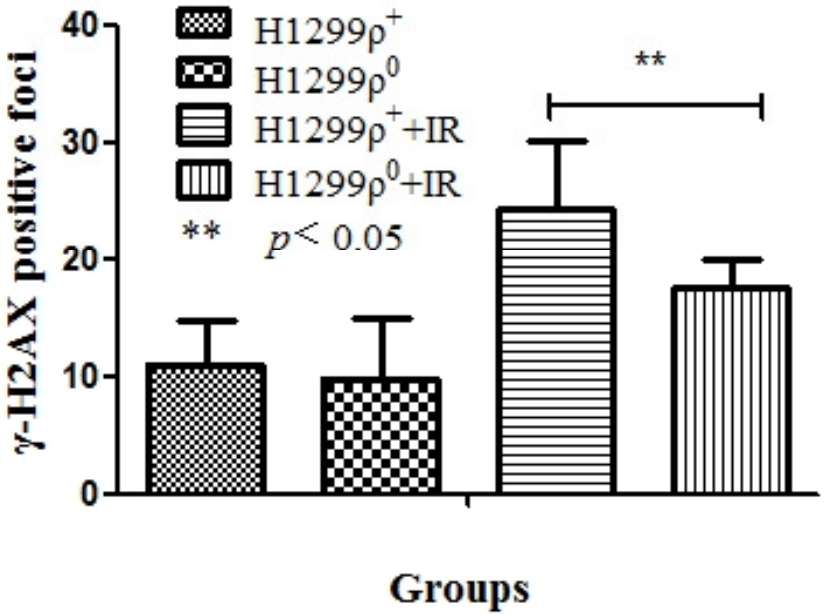




ρ0 could attenuate the radiation induced apoptosis levels

(8) mtDNA depletion accelerated the repair kinetics of DNA damage induced by IR





γH2AX foci is a marker for DNA double-strand break (DSBs) repair.

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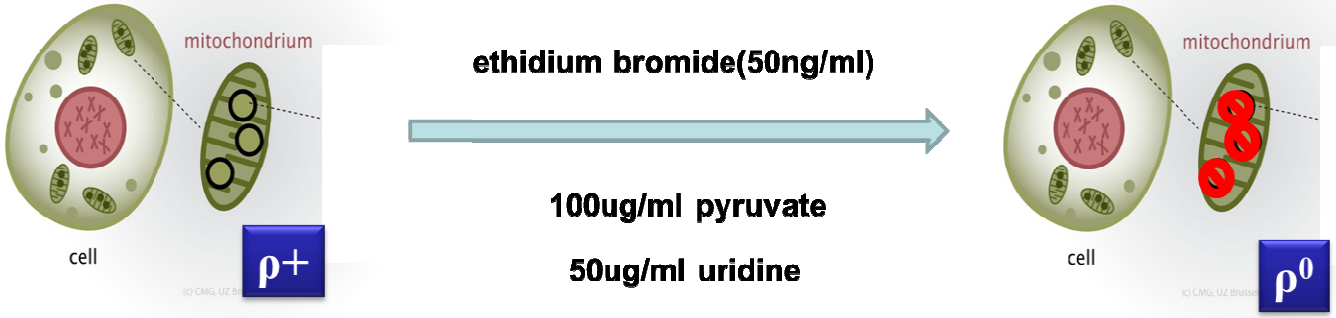
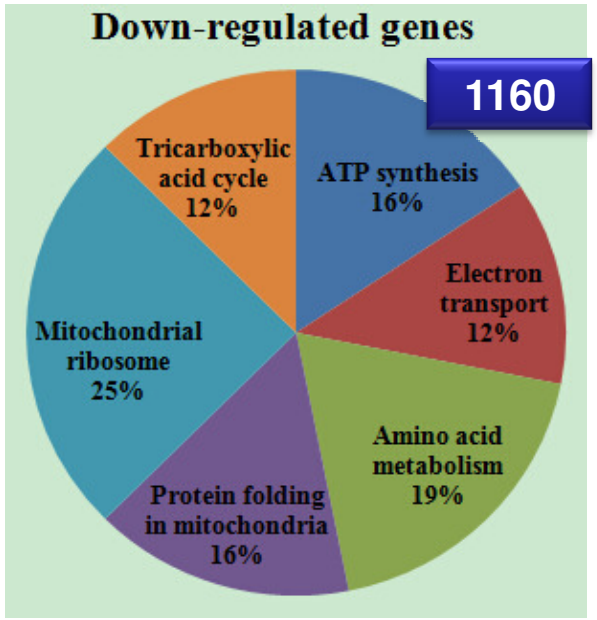
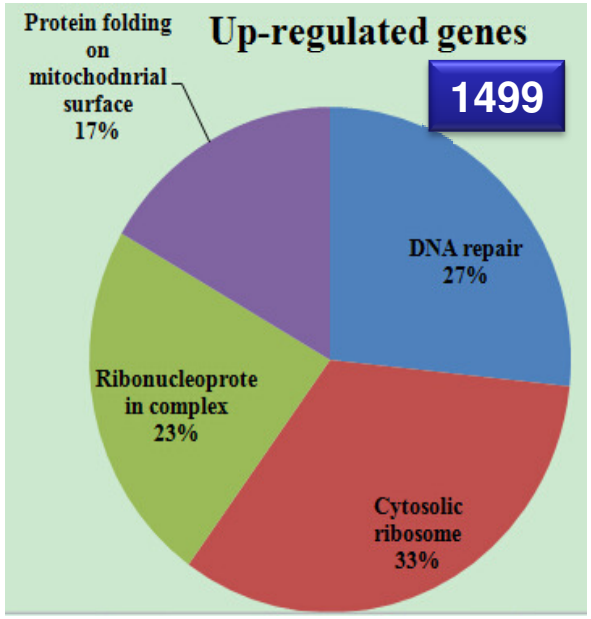
(1) GO enrichment analysis of molecular biological function



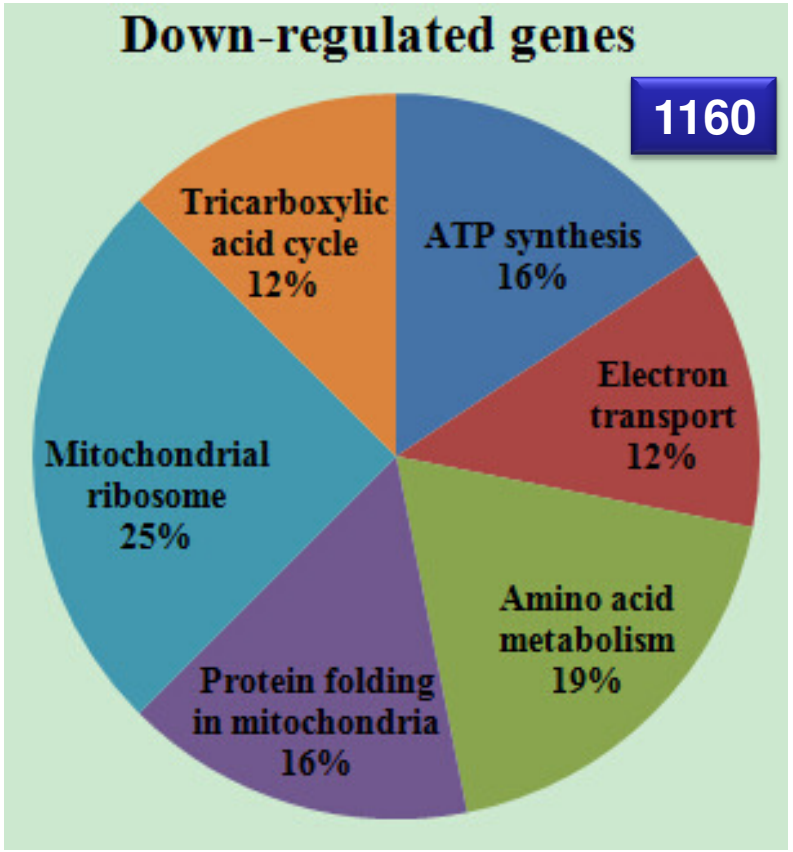
H1299 cell





fold changefc≥3，P< 0.05

(1) GO enrichment analysis of molecular biological function



Mitochondrial function related genes

ATP synthesis

The electron transport

Amino acid metabolism

Mitochondrial protein folding

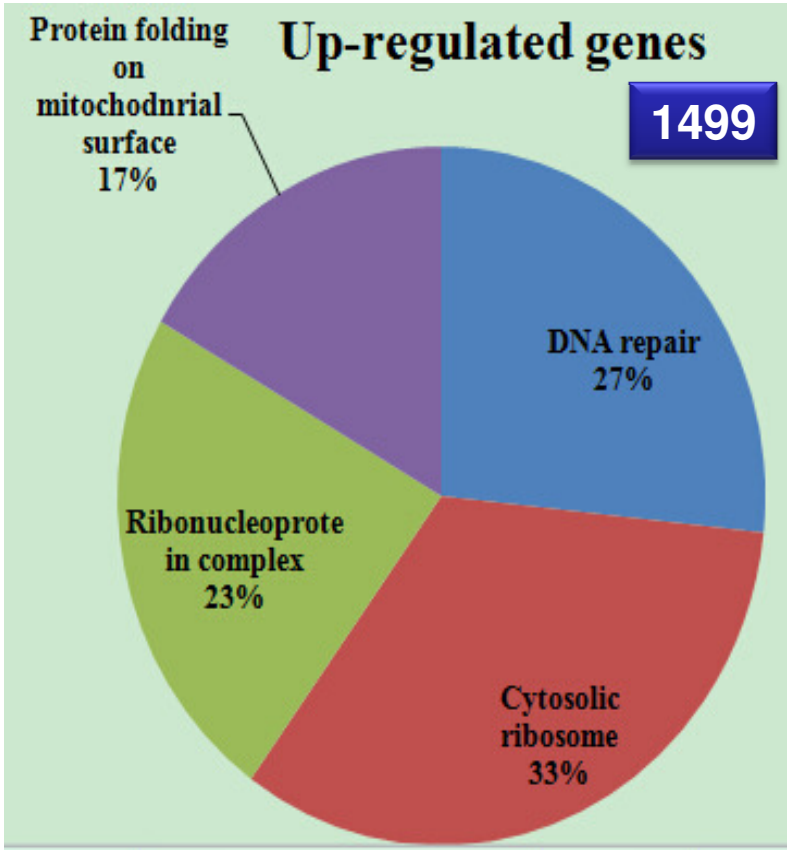
The citric acid cycle (TCA)

(1) GO enrichment analysis of molecular biological function

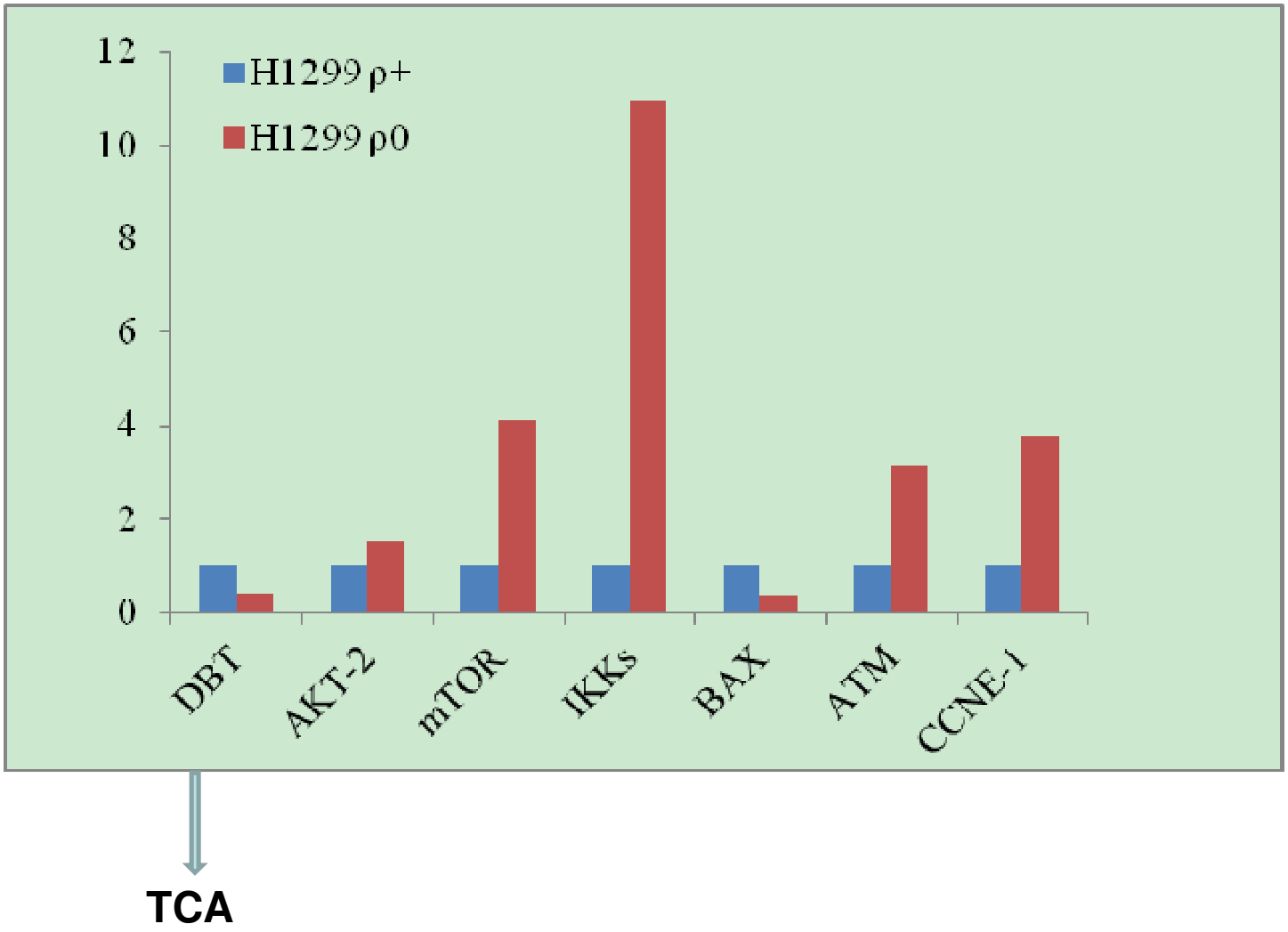
DNA repair

Ribonucleoprotein complex

Mitochondrial surface protein folding

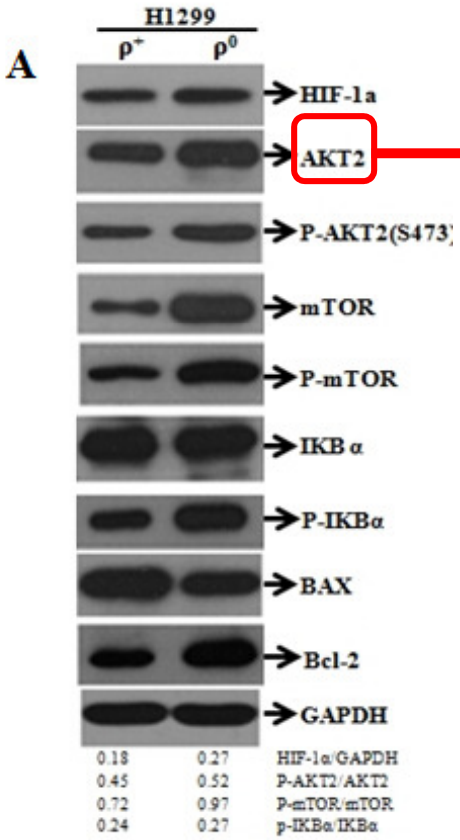


(2) Gene chip real-time PCR validation results

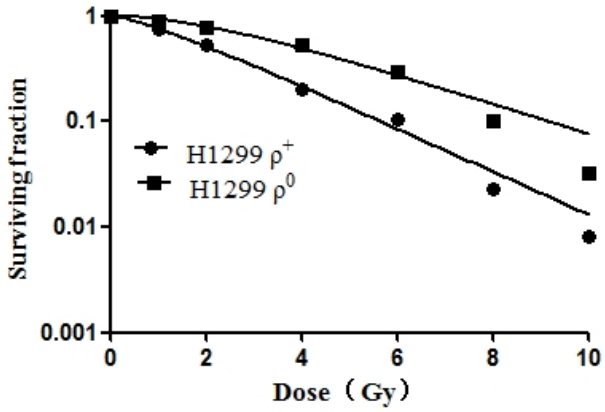


(3) NFkB /PI3K/AKT2/mTOR retrograde signaling pathway

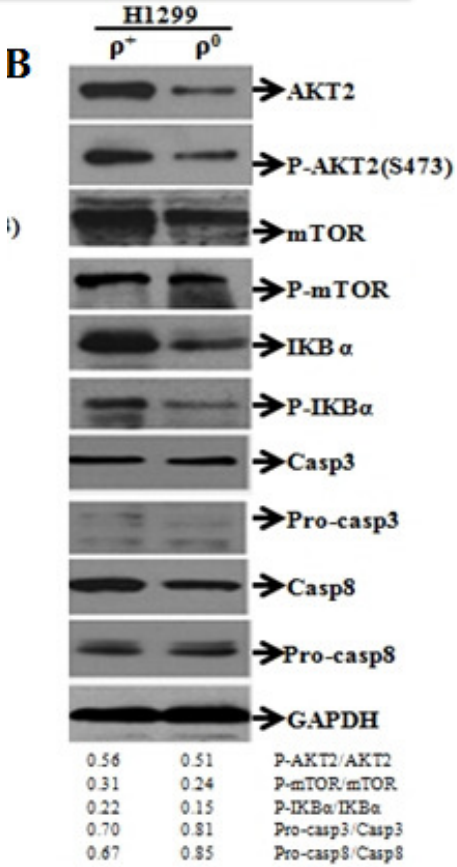
6Gy



AKT2 is highly expressed in many cancers



6Gy+AKT2 Inhibitor MK-2206 (1umol/L)



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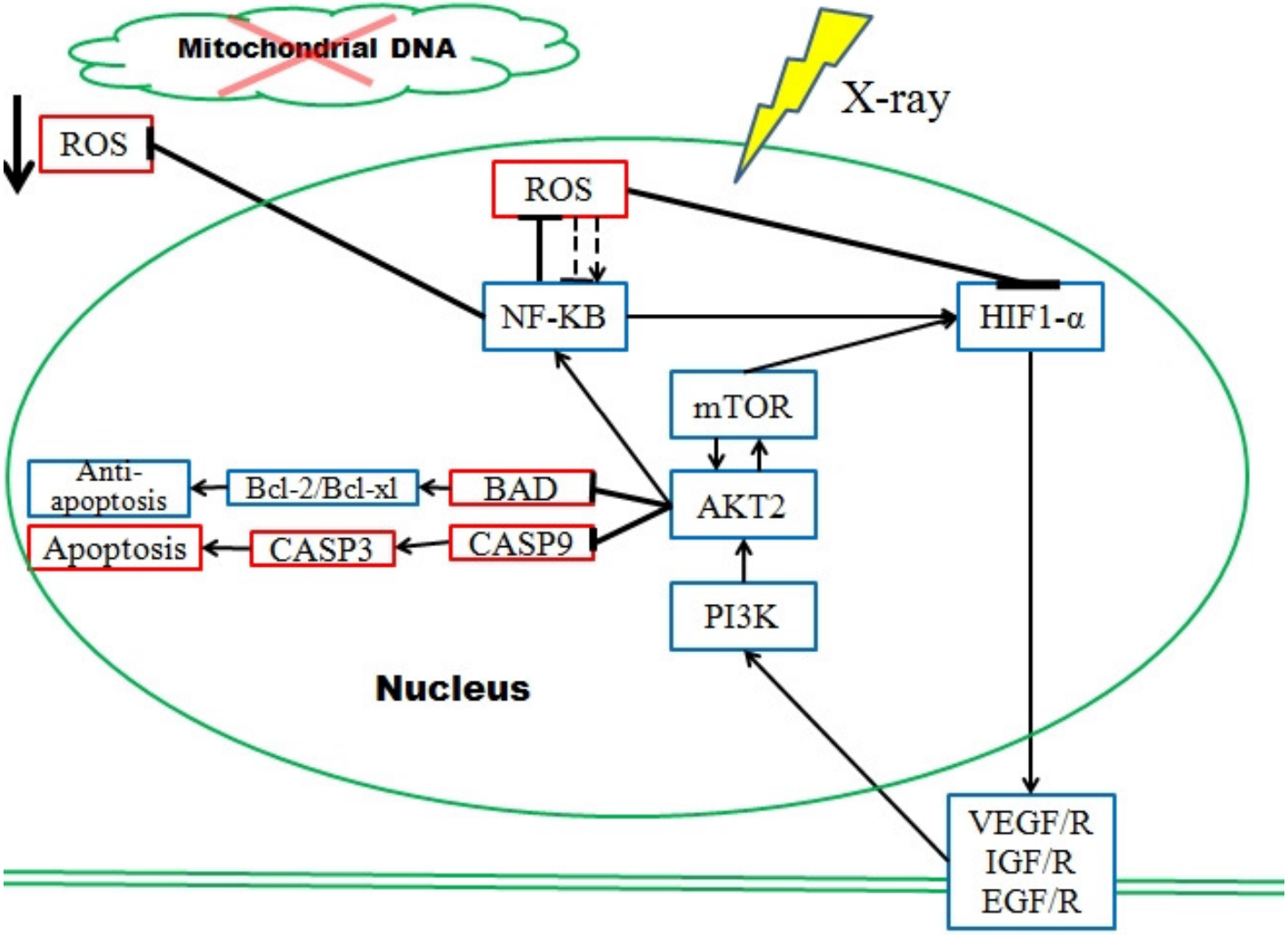
Mitochondrial DNA
X-ray
ROS
ROS
NF-KB
HIF1-α
mTOR
Anti-apoptosis
Bcl-2/Bcl-xl
BAD
AKT2
Apoptosis
CASP3
CASP9
PI3K
Nucleus
VEGF/R
IGF/R
EGF/R

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Anqi Yao

Yuexiao Qi

Li Lin

Shan Lu

National Natural Science Foundation of China

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