L'inibizione della Gliossalasi I induce apoptosi in cellule MCF-7 irradiate attraverso un nuovo meccanismo mediato da Hsp27, p53 ed NF-kB

[a]Cinzia Antognelli, [b]Isabella Palumbo, [a]Vincenzo N. Talesa, [b]Cynthia Aristei

[a]Dipartimento di Medicina Sperimentale, Università degli Studi di Perugia
[b]Dipartimento di Scienze Chirurgiche e Biomediche, Università degli Studi e Azienda Ospedaliera di Perugia

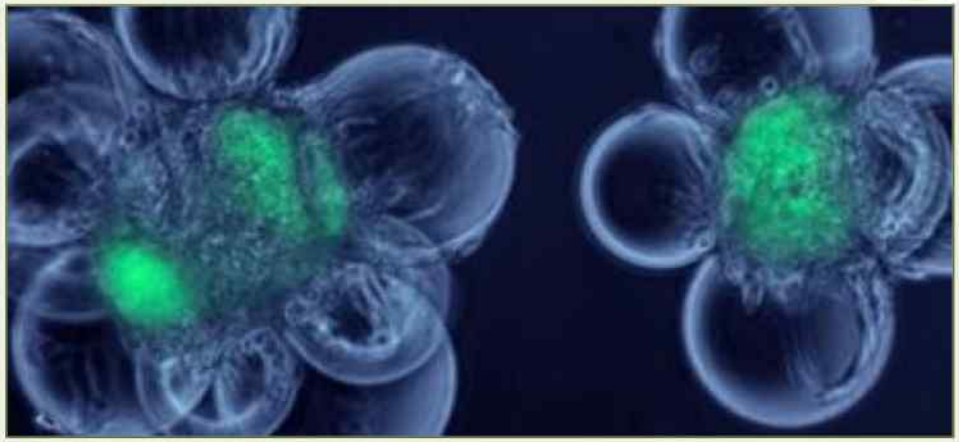
INTRAOPERATIVE RADIOTHERAPY WITH ELECTRONS TRIAL(ELIOT)

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial.
Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B.
Lancet Oncol. 2013;14(13):1269-77. doi: 10.1016/S1470-2045(13)70497-2.

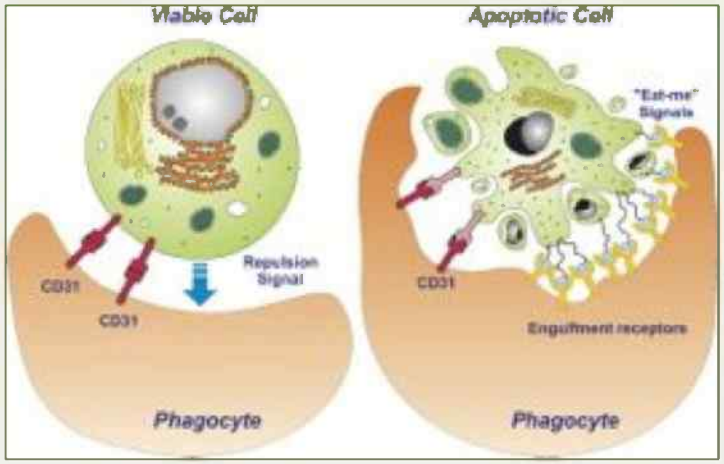
Long-term side effects and cosmetic outcome in a pool of breast cancer patients treated with intraoperative radiotherapy with electrons as sole treatment.
Leonardi MC, Ivaldi GB, Santoro L, Lazzari R, Ferrari A, Morra A, Caldarella P, Burgoa L, Bassi FD, Sangalli C, Rotmensz N, Luini A, Veronesi U, Orecchia R.
Tumori. 2012 98(3):324-30. doi: 10.1700/1125.12400.

Intraoperative radiotherapy during **breast** conserving surgery: a study on 1,822 cases treated with electrons.
Veronesi U, Orecchia R, Luini A, Galimberti V, Zurrida S, Intra M, Veronesi P, Arnone P, Leonardi MC, Ciocca M, Lazzari R, Caldarella P, Rotmensz N, Sangalli C, Sances D, Maisonneuve P.
Breast Cancer Res Treat. 2010;124(1):141-51. doi: 10.1007/s10549-010-1115-5.

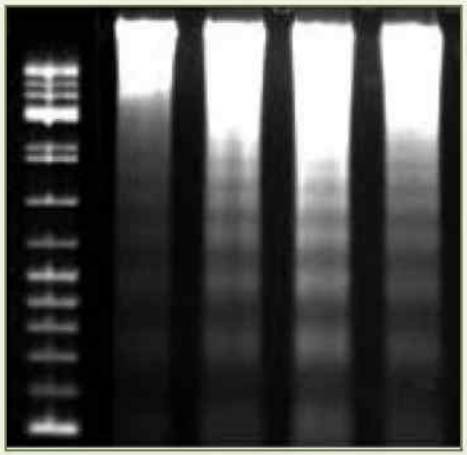
MORTE CELLULARE PROGRAMMATA: APOPTOSI



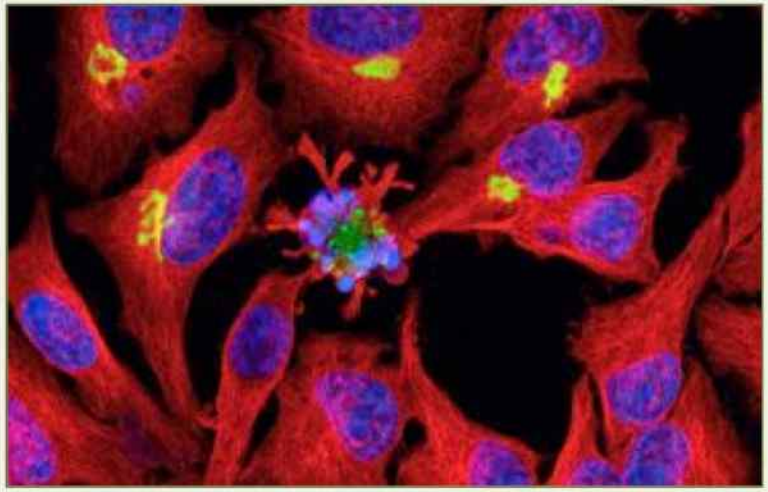
Cell blebbing



Phagocytosis



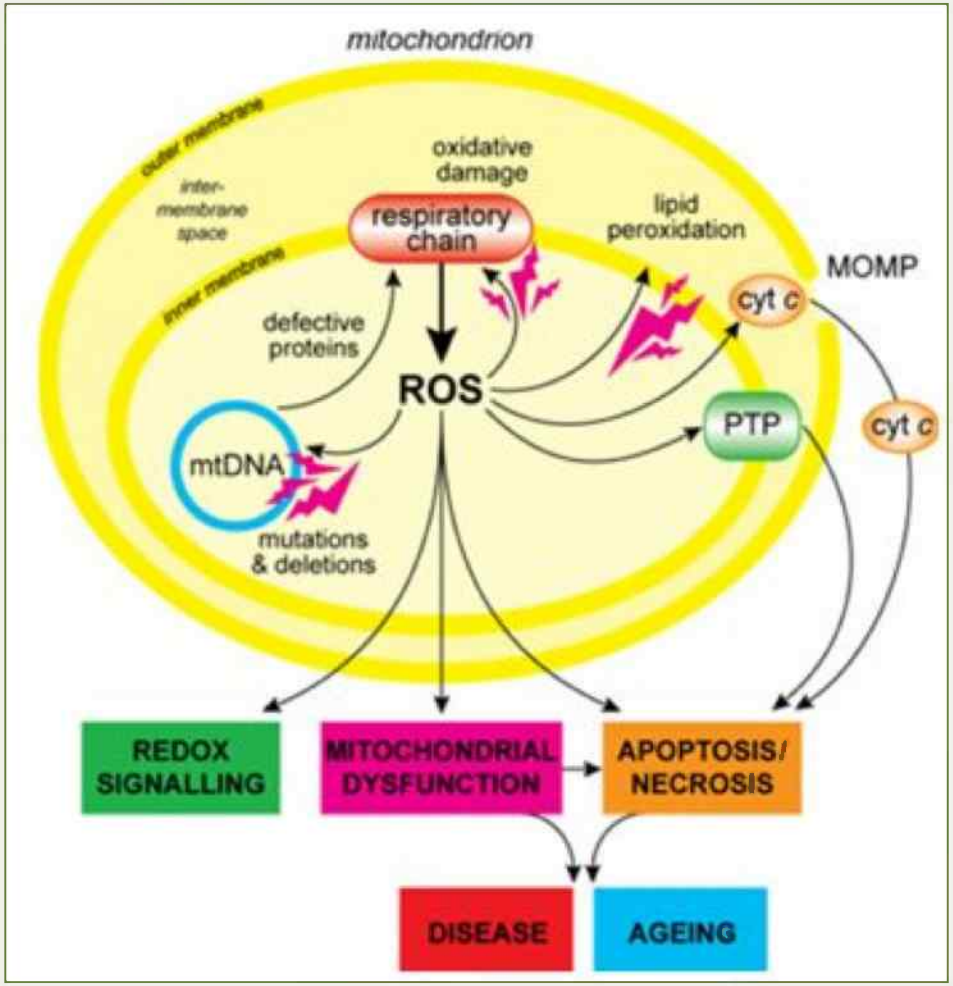
DNA laddering



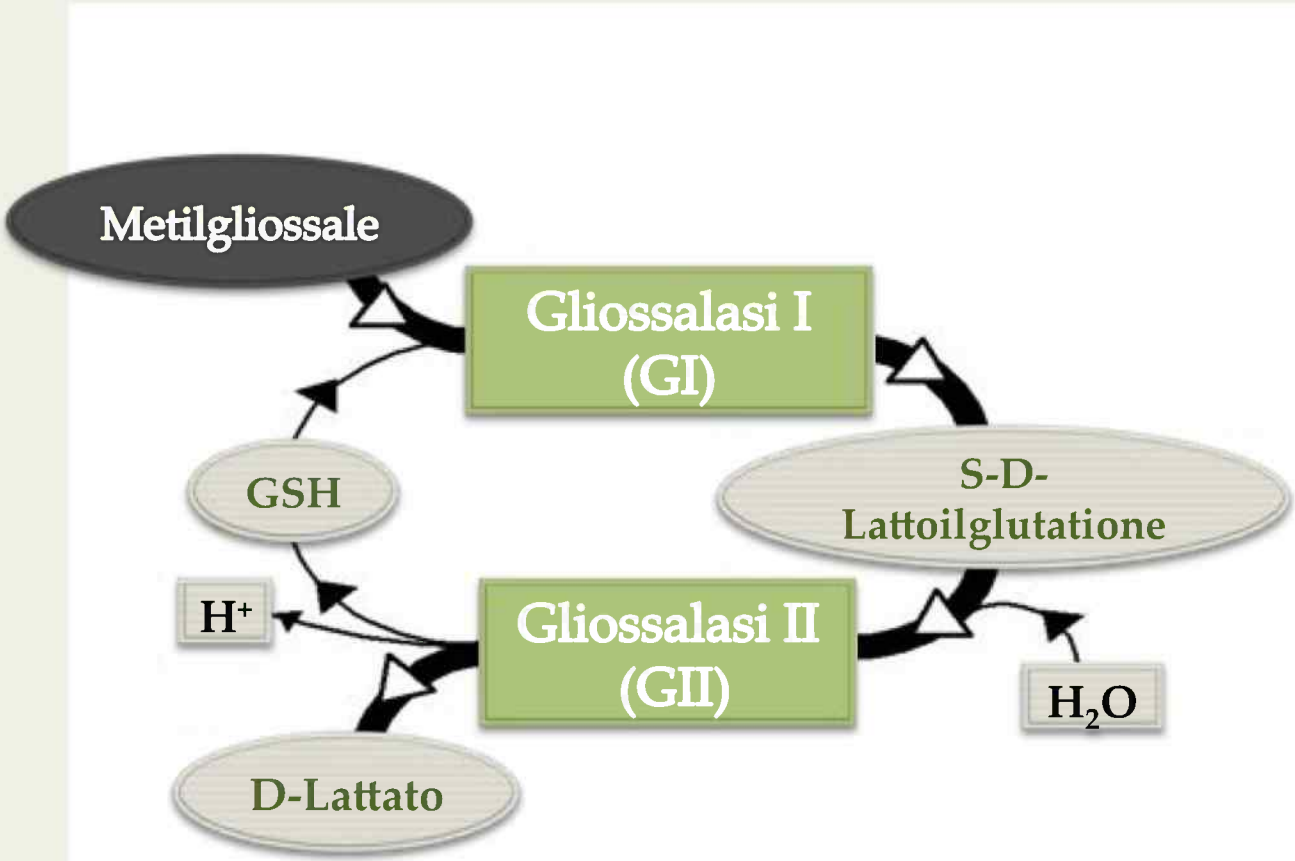
F-actin - Immunofluorescence

LE SPECIE REATTIVE DELL'OSSIGENO (ROS)

		
Oxygen	Superoxide anion	Peroxide
O_2	$\cdot O_2^-$	$\cdot O_2^{-2}$
		
Hydrogen Peroxide	Hydroxyl radical	Hydroxyl ion
H_2O_2	$\cdot OH$	OH^-

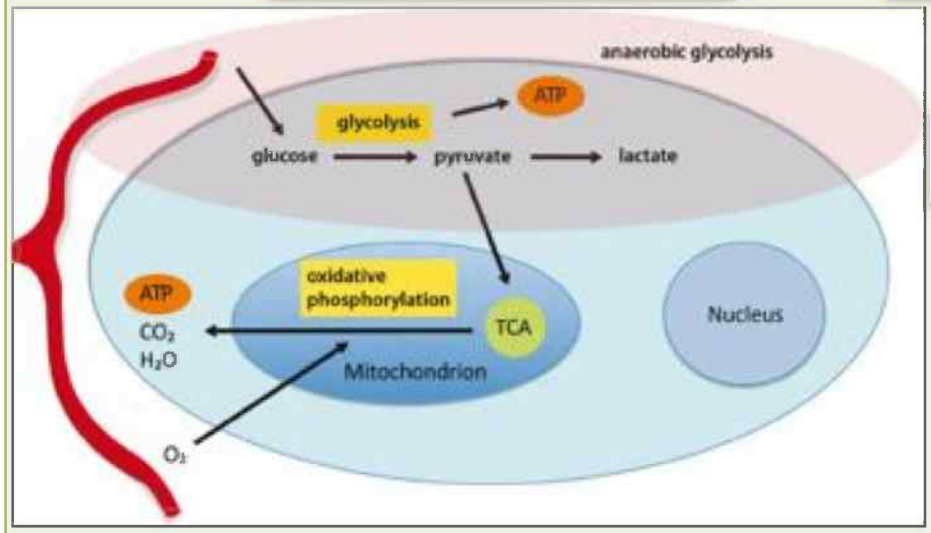


IL SISTEMA DELLE GLIOSSALASI

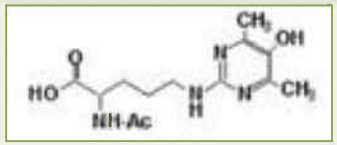


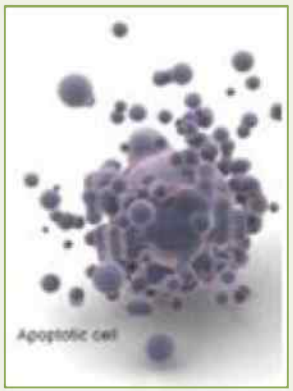
METILGLIOSSALE (MGO)

GLICOLISI → **MGO** → **AGEs**



ARGPIRIMIDINA (AP)



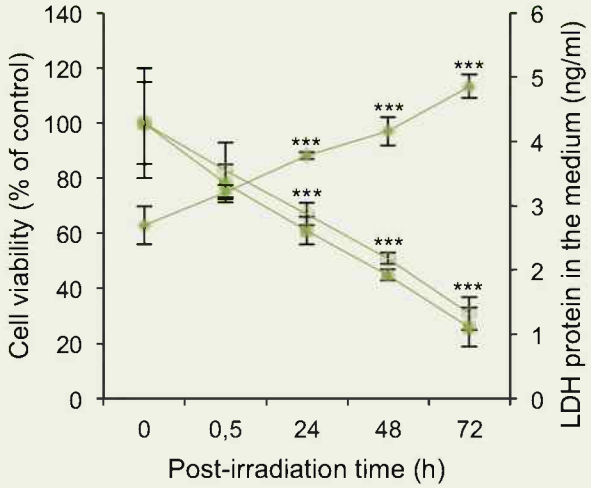


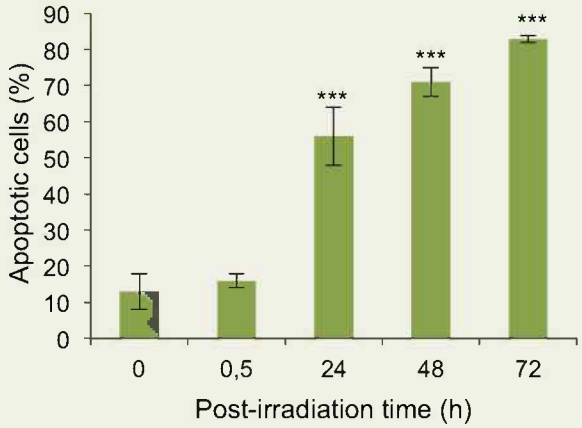
OBIETTIVO DELLA RICERCA

RUOLO DELLA GLIOSSALASI I NELL'APOPTOSI INDOTTA DALLE RADIAZIONI IONIZZANTI NELLA LINEA CELLULARE DI ADENOCARCINOMA MAMMARIO UMANO ORMONO-RESPONSIVA, MCF-7, MODELLO CELLULARE DI CANCRO DELLA MAMMELLA A STADIO INIZIALE, ESPOSTA ALLA SINGOLA DOSE DI 21 Gy, COME DA PROTOCOLLO ELIOT

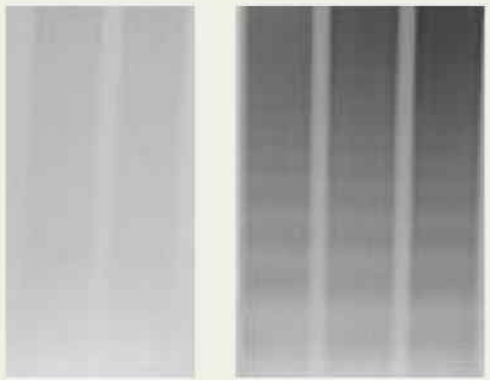
Le radiazioni ionizzanti (IR) inducono citotossicità in cellule MCF-7 attraverso l'induzione di apoptosi

RISULTATI



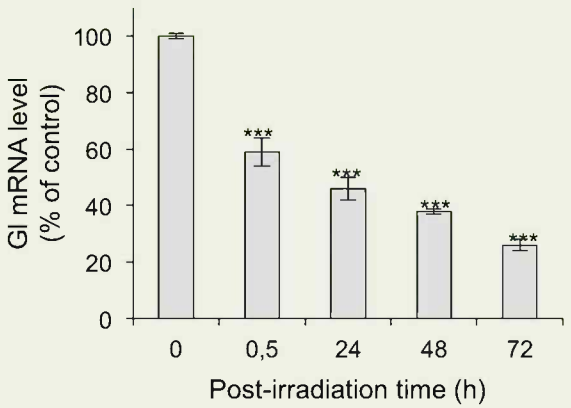


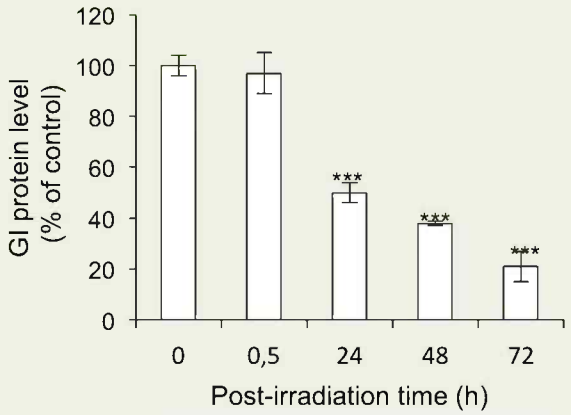
***p < 0.001

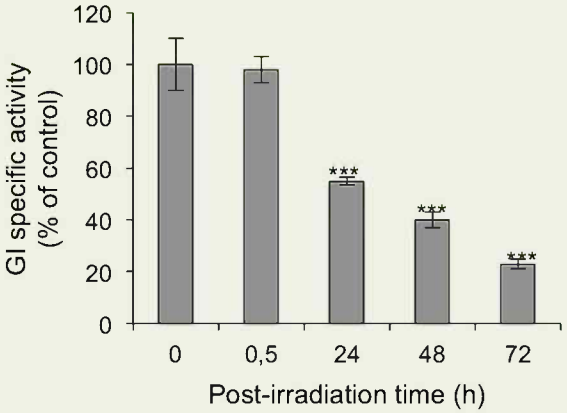


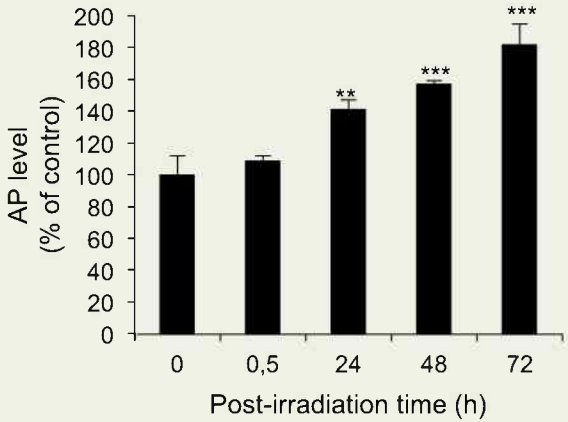
Effetto delle IR sul profilo di espressione di GI e sui livelli intracellulari di Argpirimidina (AP) in cellule MCF-7

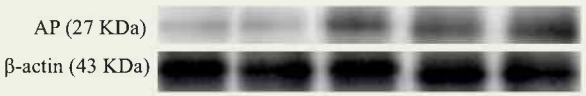
RISULTATI







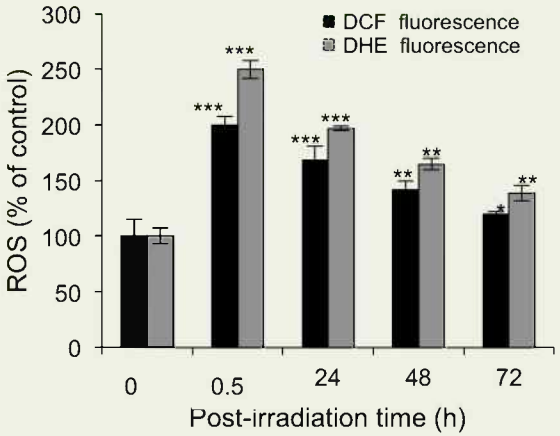


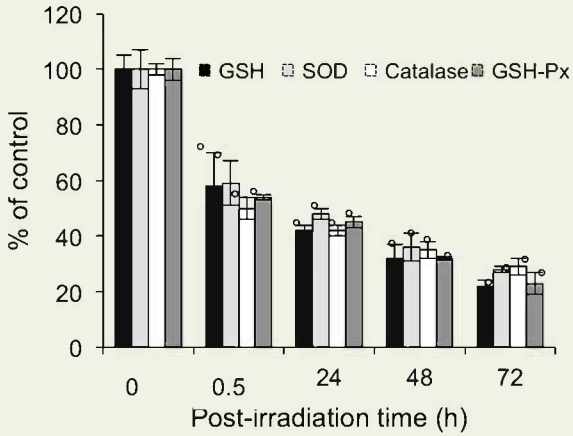


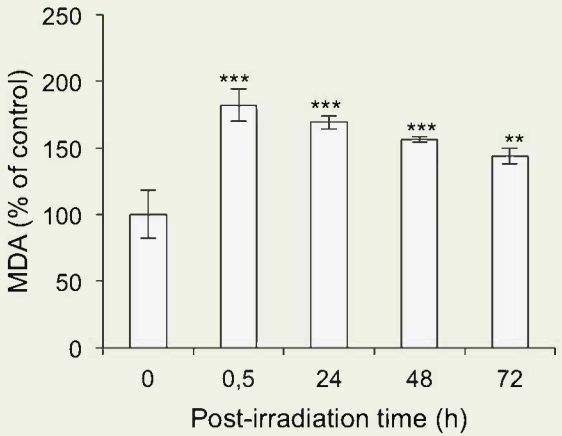
**p < 0.01, ***p<0.001

Le IR inducono stress ossidativo in cellule MCF-7

RISULTATI



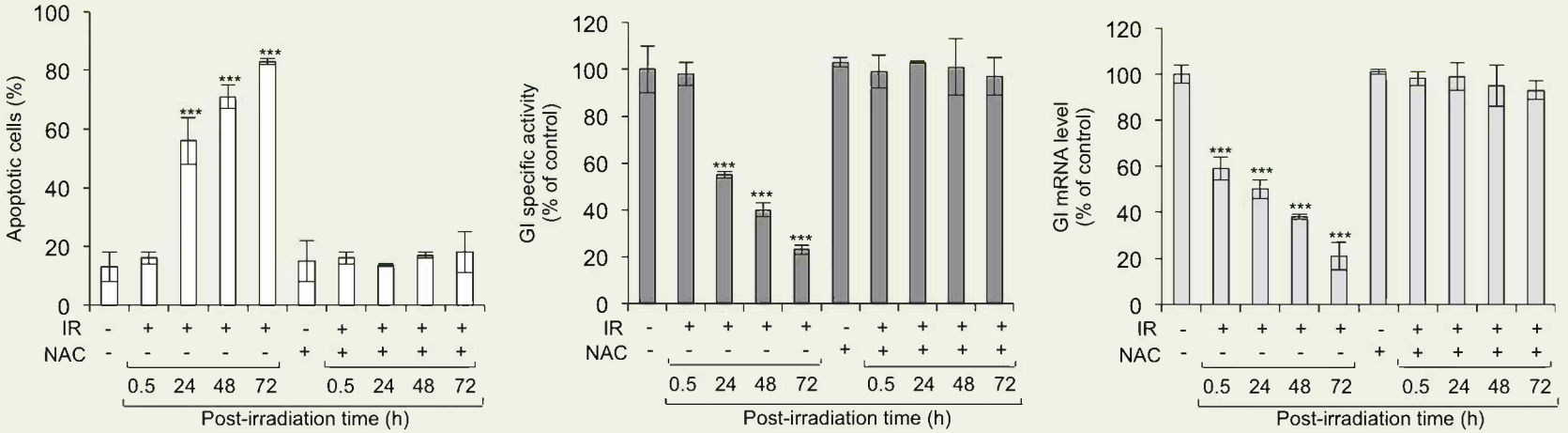


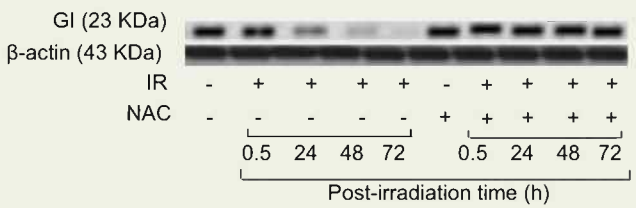


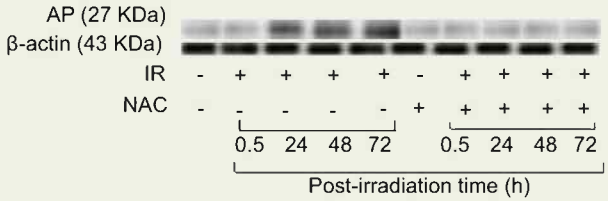
*p < 0.05, **p < 0.01, ***p or °p <0.001

L' apoptosi indotta dalle IR si realizza attraverso l'inibizione mediata dai ROS della GI e l'accumulo intracellulare di AP in cellule MCF-7

RISULTATI



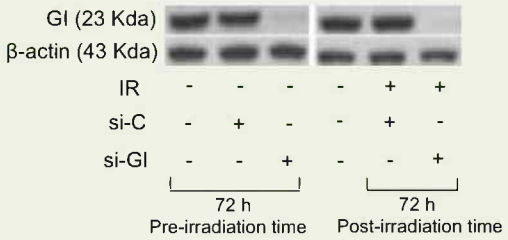


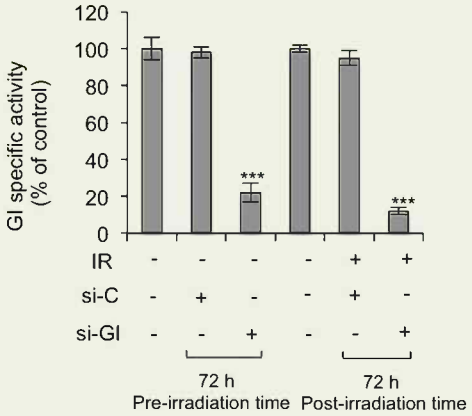


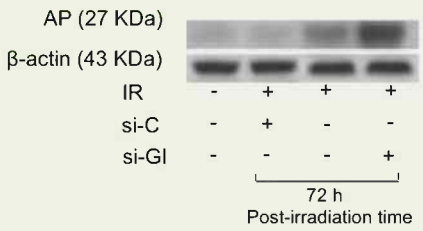
***p <0.001

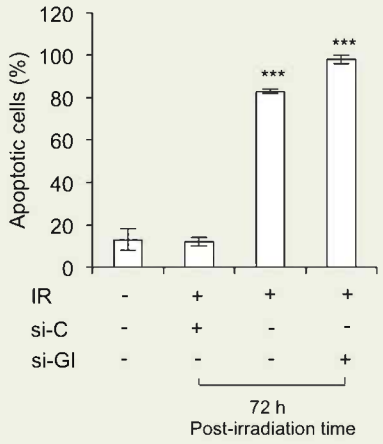
L' apoptosi indotta dalle IR si realizza attraverso l'inibizione di GI e l'accumulo intracellulare di AP in cellule MCF-7

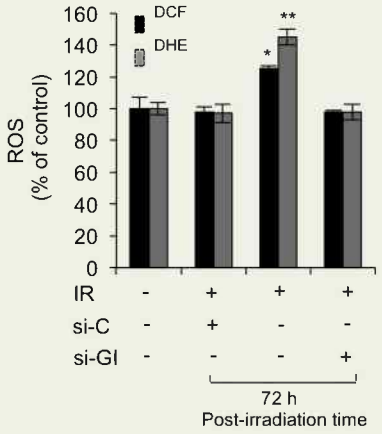
RISULTATI

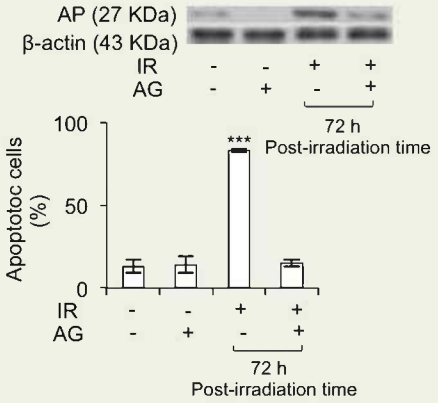








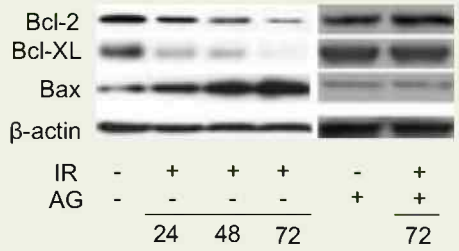


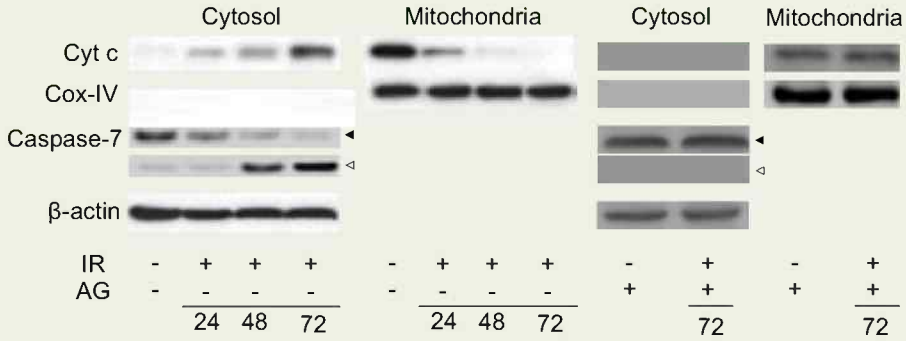


*p < 0.05, **p < 0.01, ***p <0.001

RISULTATI

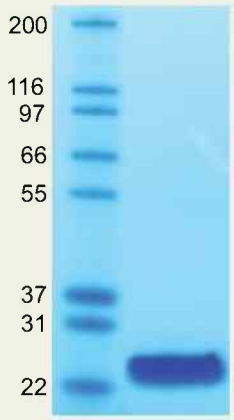
L'inibizione della GI mediata dai ROS e indotta dalle IR, accompagnata dall'accumulo di AP, dirige un pathway apoptotico mitocondriale che coinvolge NF-kB



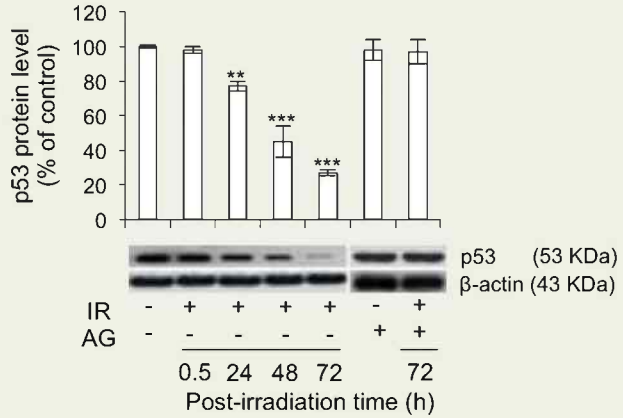


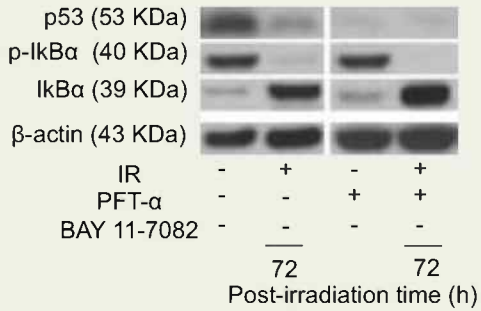
Ruolo di Hsp27 e p53 nel pathway apoptotico mitocondriale mediato dai ROS e indotto dalle IR

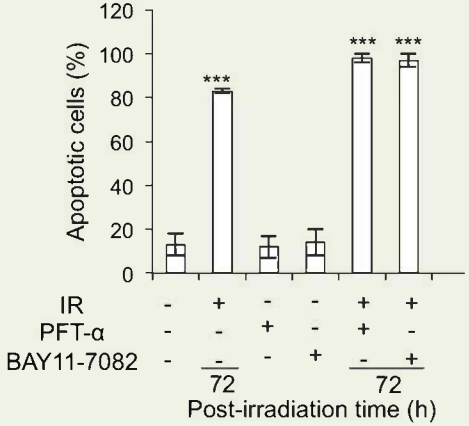
RISULTATI



1 19
27 kDa protein: PPGVDPTQVSSSLSPEGTLTV-
Human Hsp27: PPGVDPTQVSSSLSPEGTLTV-
145 165



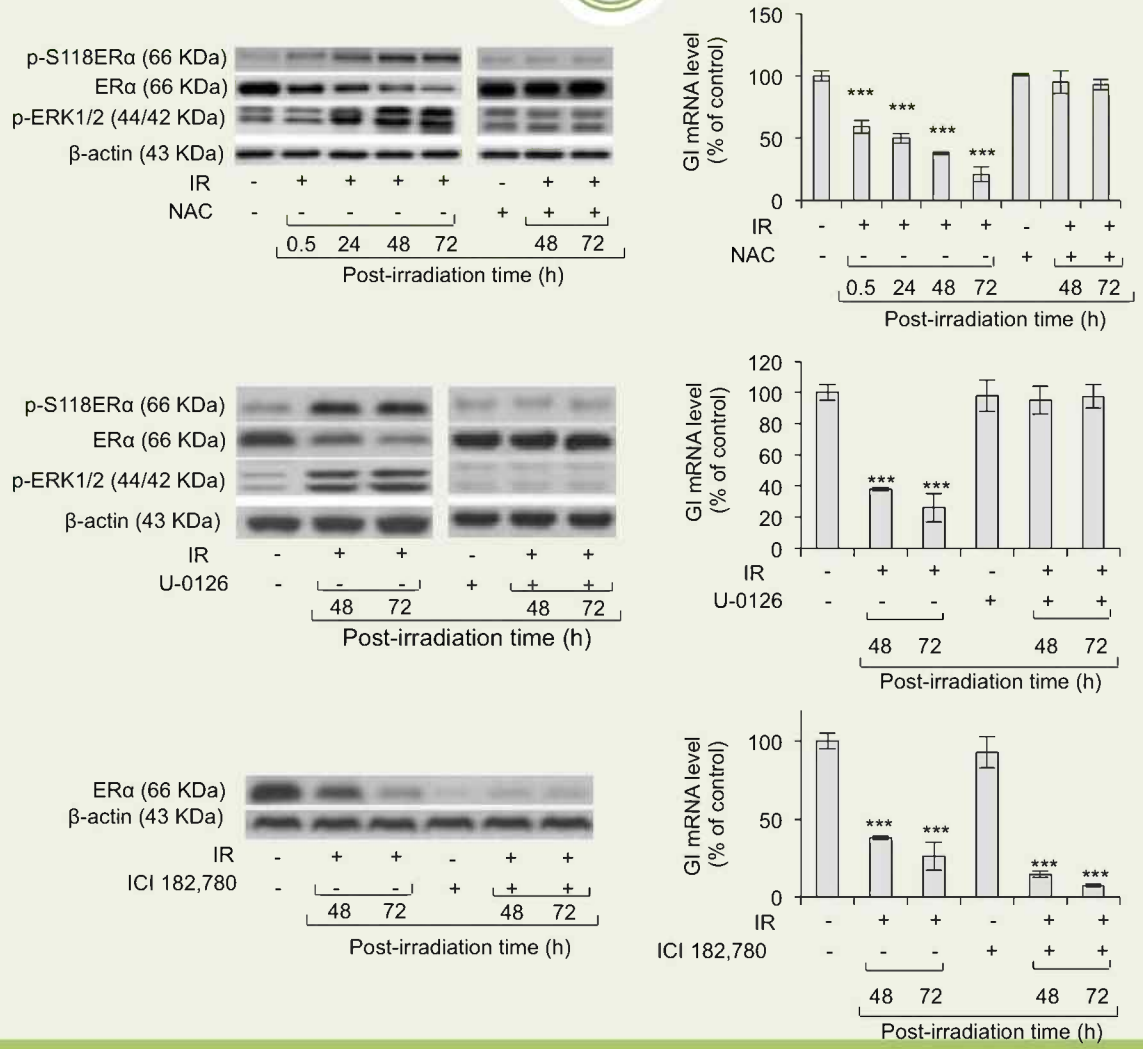




**p < 0.01, ***p <0.001

La modulazione negativa del trascritto di GI mediata dai ROS e indotta dalle IR ha luogo attraverso ERα e ERK 1/2 MAPK

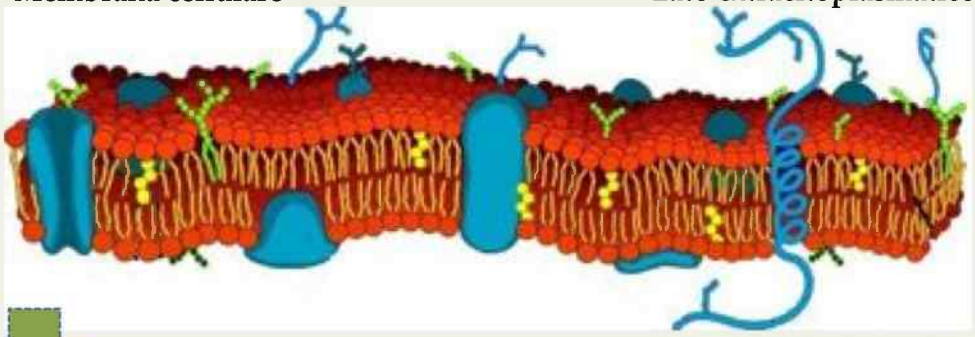
RISULTATI



MECCANISMO

Membrana cellulare

Lato extracitoplasmatico

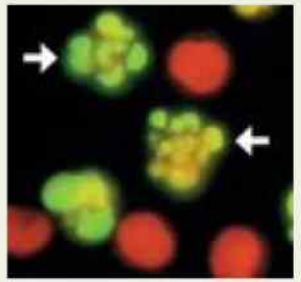


Lato citoplasmatico

ROS → GI → AP/Hsp27 → p53 → NF-kB

GI → Erk 1/2

GI → ERα



CONCLUSIONI

L'efficacia apoptogenica della dose di radiazioni ionizzanti impiegata nel protocollo ELIOT in cellule ormono-responsive a stadio iniziale di cancro della mammella supporta, *in vitro*, l'osservata efficacia di tale terapia in pazienti con tipizzazione bio-patologica favorevole.

... Graxie ...

Azienda Ospedaliero - Universitaria di Perugia