

# Overexpression of GDF-15 Increases Radiosensitivity of Breast Cancer Cells

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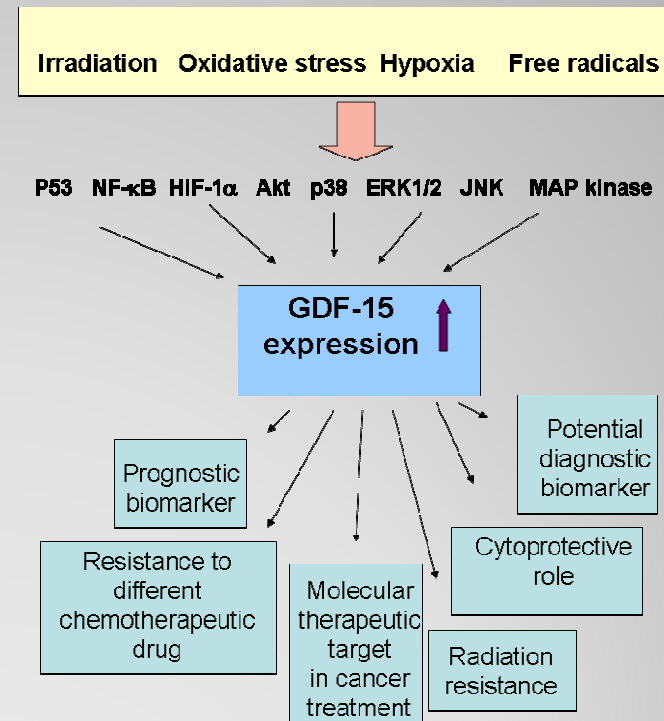
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# GDF-15 plays a role:

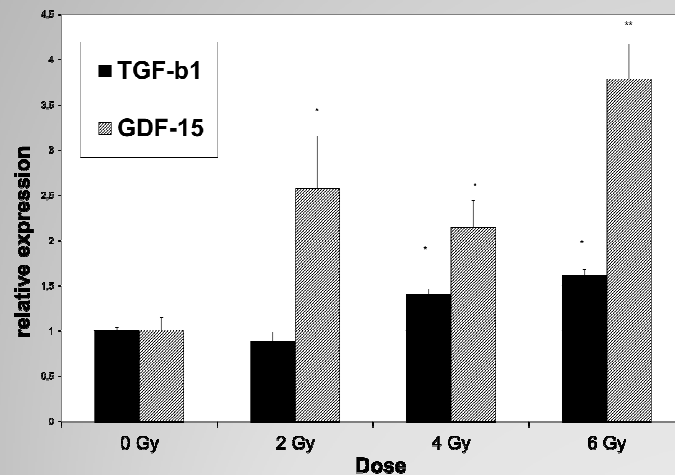
- in control of stress responses
- in cancer development and progression
- on antitumorigenic actions, its expression is crucial for the chemopreventive effects of various compounds in prostate and cancer.
- in malignant melanomas, GDF-15 is highly overexpressed and it is able to mimic VEGF in the neovascularization in the tumor site
- in inhibition of NKT-cell-mediated cytotoxicity, similar to the effects of TGF- $\beta$  in malignant glioma.
- associated with radioresistant phenotype in head and neck cancer



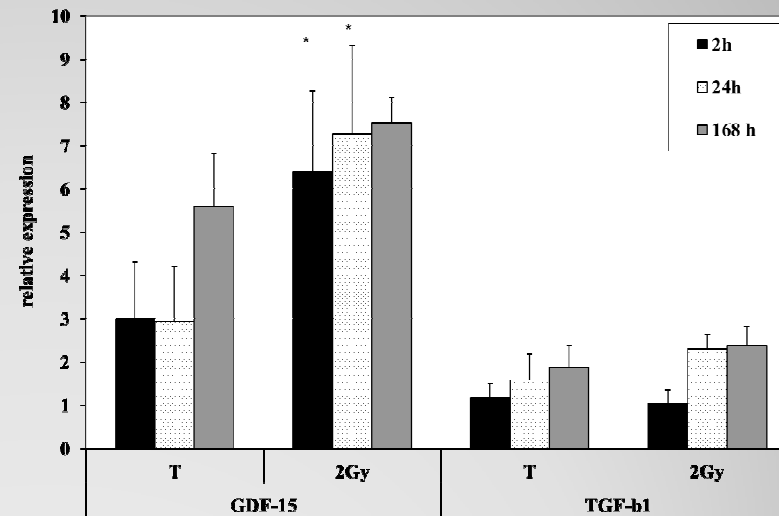
Hegyesi et al, "[Breast Cancer - Recent Advances in Biology, Imaging and Therapeutics](#)" 2011

# Radiation induced expression of GDF-15 and TGF- $\beta$ 1 in mouse breast cancer cell

- In vitro



- In-vivo

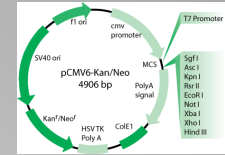


GDF-15 is an early radiation response gene

# Aim

The purpose of this study was to investigate the effect of **overexpression of GDF15 gene** on proliferation and radiosensitivity of breast cancer cells in vitro and in vivo.

# Experimental models



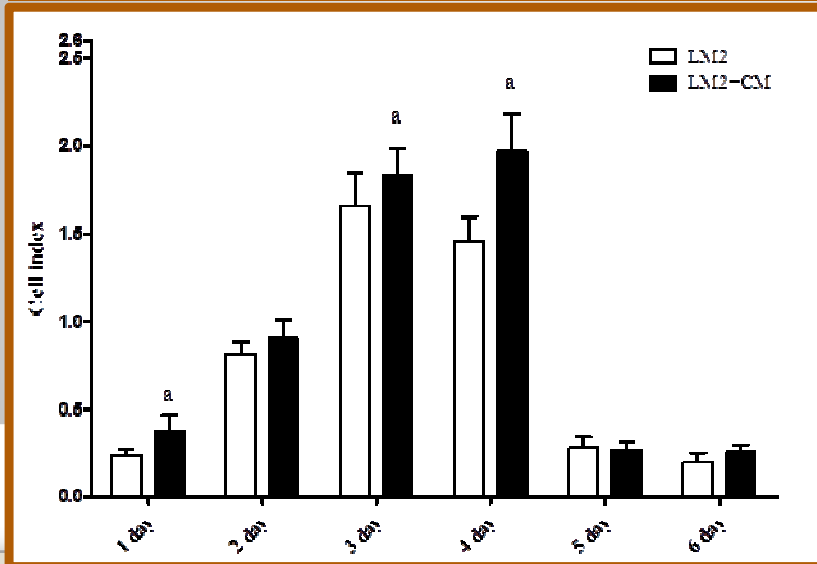
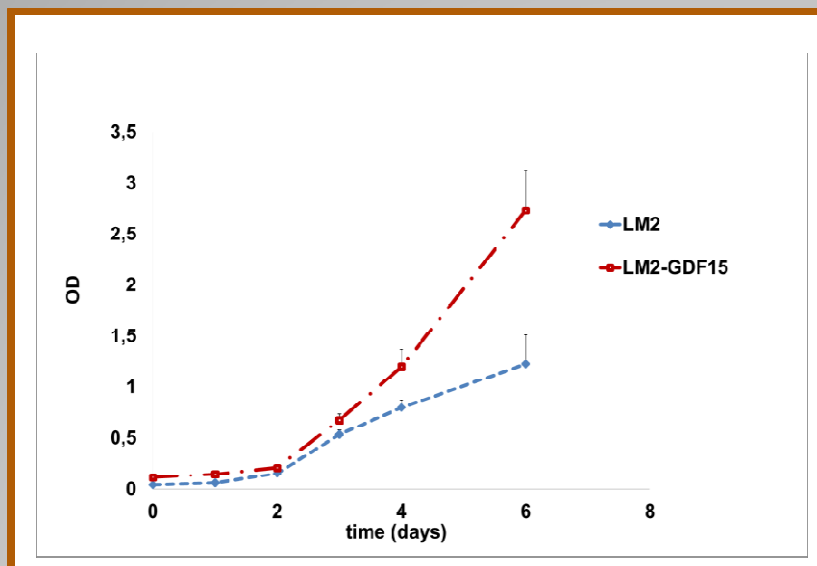
## In vitro:

- A mouse breast cancer LM2 cell line with transfection of full-length mouse GDF15 cDNA was established
- LM2 cells transfected with the empty vector or the expression plasmid for GDF15-GFP. Transfected cells were selected with puromycin and with expression of GFP, cells were cultured and maintained for long time.

## In vivo:

- in the syngeneic LM2-GDF15 murine breast cancer model was used in vivo

## Results: The effects of GDF-15 on the survival of mice breast carcinoma cells in-vitro

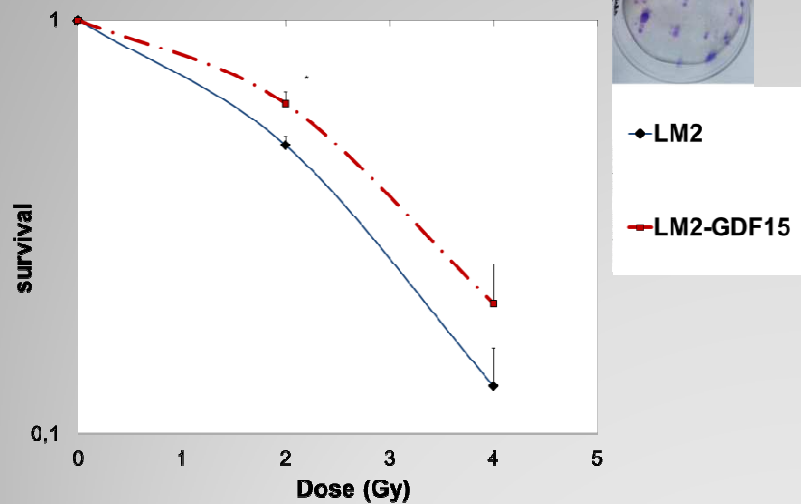


- LM2 cells: mice breast cancer cells that express empty vector
- LM2-GDF-15: cells express high amount of GDF-15
- LM2-CM: Conditioned medium of LM2-GDF-15 cells

Endogenous overexpression of GDF-15 induces proliferation  
Treatment with GDF-15 containing medium enhances the growth of cells

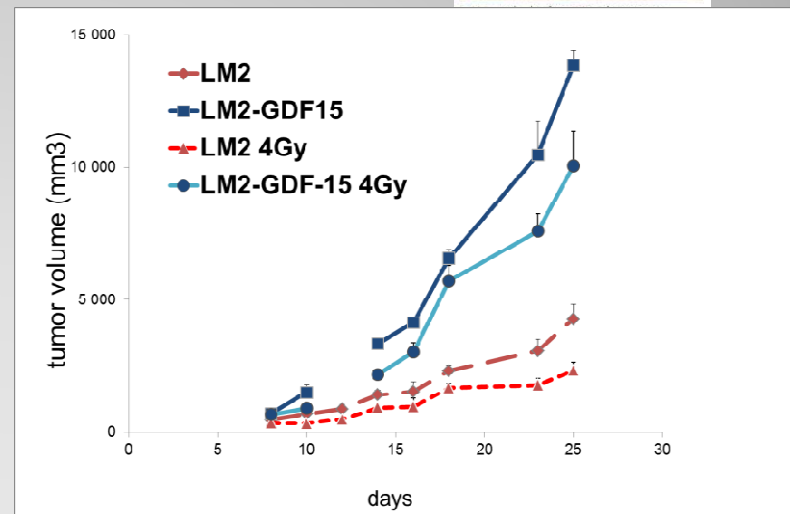
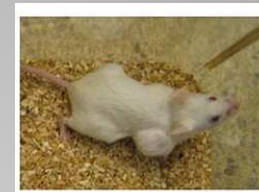
# Results : Radiation Survival

- In-vitro



Overexpression of GDF-15 promotes the survival of tumor cells exposed to IR

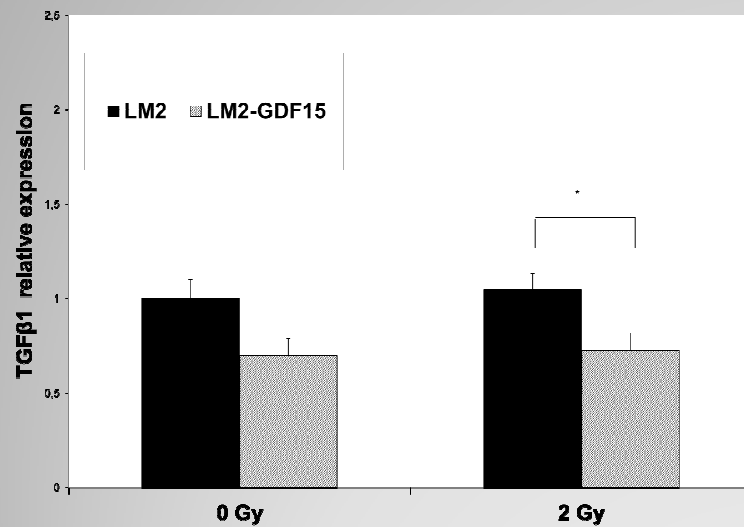
- In-vivo



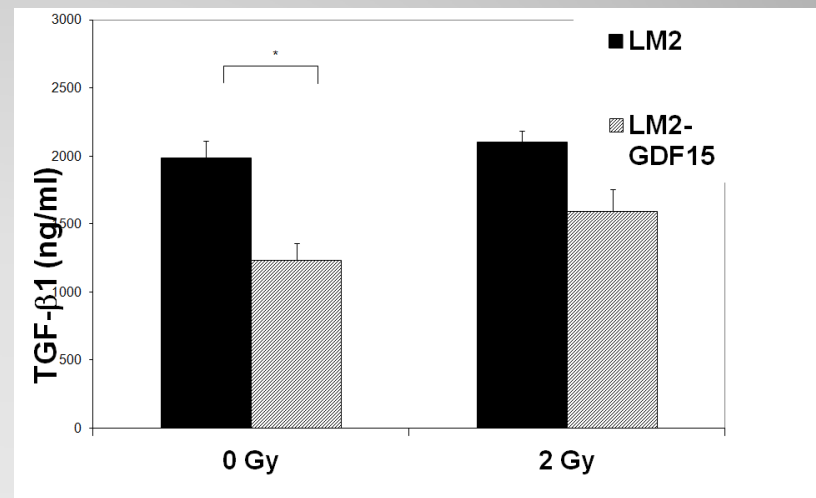
Tumors derived from GDF-15 transfected LM2 cells showed enhanced tumorigenicity in BalB/c mice compared with vector-transfected LM2 cells.

# Results: Radiation induced expression of TGF- $\beta$ 1 modulated by overexpression of GDF-15

- qPCR



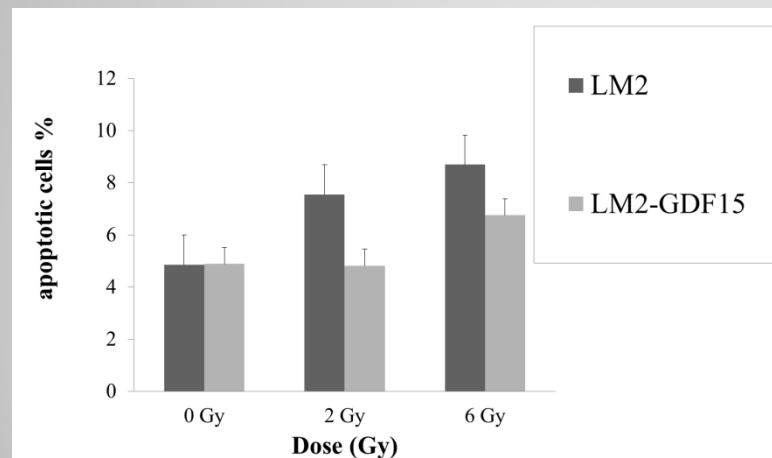
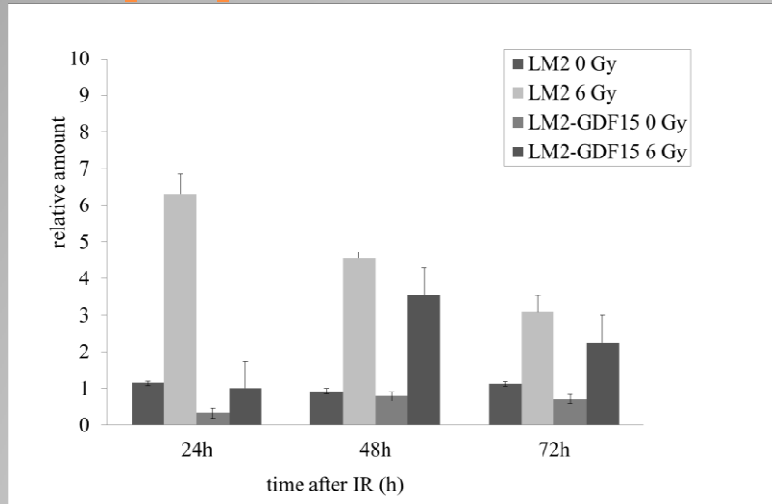
- ELISA



GDF-15 inhibits the expression of TGF- $\beta$ 1



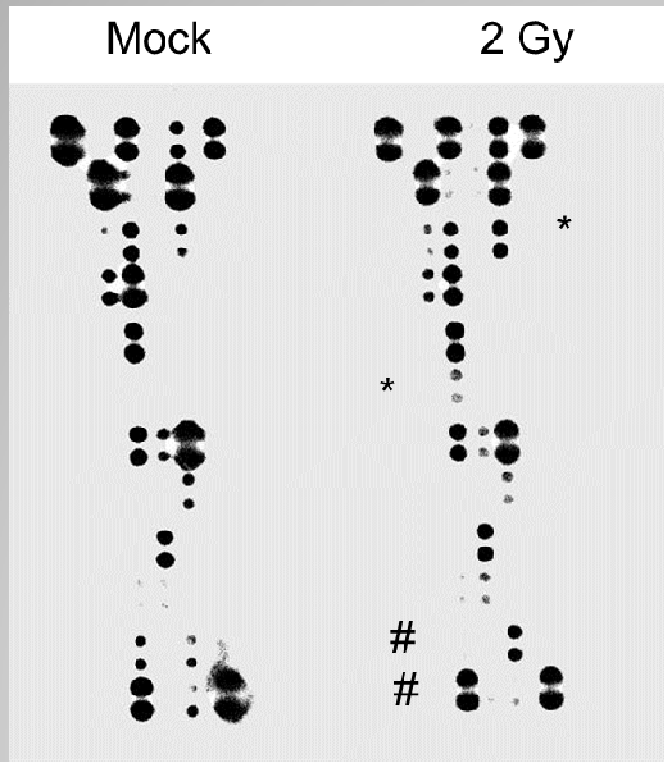
# Radiation -induced mitochondrial damage and apoptosis modulated by GDF-15



- Treatment of cells with IR showed increased mitochondrial DNA deletion in 24 h
- Overexpression of GDF-15 inhibited the radiation induced mitochondrial DNA deletion.
- Overexpression of GDF-15 inhibits IR-induced cell apoptosis

Suggests the protective role of GDF-15 in IR mediated deletion of mitochondrial DNA and in IR induced apoptosis

# IR induced serum proteins



- Mouse Cytokine Array (R&D Systems) was used to simultaneously detect the relative levels of 40 different cytokines, chemokines in plasma fraction of tumor – bearing animal 24h later of irradiation
- \*TNF- $\alpha$  and IL-10 was elevated
- #CXCL-12 and IL-2 was inhibited by IR

## Summary

- GDF-15 is a radiation response gene
- Overexpression of GDF-15 enhanced the proliferation of LM2 cells in vitro
- GDF-15 caused forced tumor growth in vivo
- GDF-15 treatment increased the survival rate of LM2 in vitro
- IR induced apoptosis in LM2 cells was associated to the generation of mitochondrial DNA deletion.
- Overexpression of GDF-15 reduced the IR caused DNA damage resulting in the prevention of apoptotic cell death.
- By overexpression of GDF-15, the expression of TGF- $\beta$ 1 was inhibited; this suggested that TGF- $\beta$ 1 was one of the a molecular target of GDF-15 in breast cancer cells.

# Conclusion

GDF-15 plays a role in radioresistance of LM2 mouse breast cancer cells via effecting survival, inhibiting of radiation induced mitochondrial damage and apoptosis and by inhibiting of TGF- $\beta$ 1 related cytotoxic action

**Thank you for your attention!**  
**NRIRR**



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