The Integrated Stress Response releases the oncoprotein in TP53

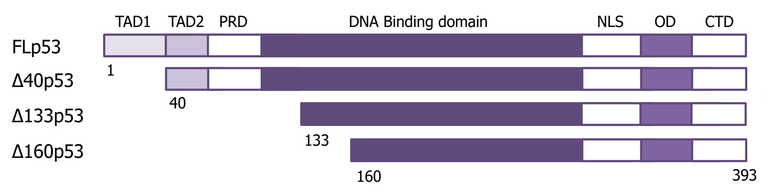
Ana Catarina Ramalho[1,2], Maria José López-Iniesta[2], Rafaela Lacerda[1], Shrutee N. Parkar[2], Luísa Romão[1] & Marco M Candeias[1,2]

[1]Department of Human Genetics, National Institute of Health Doutor Ricardo Jorge, Lisbon, Portugal,

[2]MaRCU – Molecular and RNA Cancer Unit, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Introduction

p53 α isoforms Transcription factors activated in response to stress



Alternative translation
of isoforms with internal initiation sites

Tumour suppressor
- Apoptosis
- Cell Cycle Arrest
- Senescence
- DNA Repair

Oncogenic
- Cell survival
- Proliferation
- Invasion

Overexpressed in cancer cells

Endoplasmic reticulum stress, nutrient deprivation, other stresses.

Integrated Stress Response (ISR)
Mainly a pro-survival program

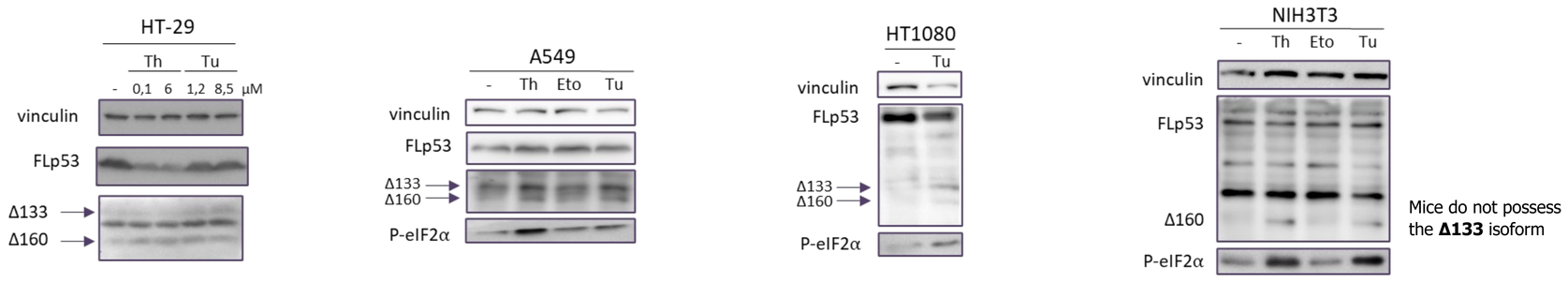
↓ specialized kinases (PERK,GCN2, PKR and HRI)

phosphorylation of **eIF2α** → **Alternative translation** of specific mRNAs with uORFs or IRESs (e.g. ATF4)

⊥ eIF2-GTP/Met-tRNAi ternary complex formation → Global reduction of protein synthesis

Results

1. ISR promotes the translation of Δ160p53 and Δ133p53



Cell lines: colon carcinoma | lung adenocarcinoma | fibrosarcoma | mouse embryonic fibroblast

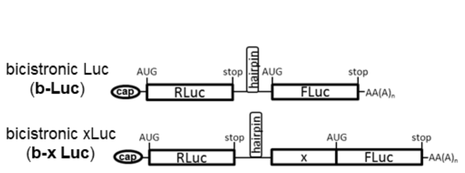
Mice do not possess the **Δ133** isoform

ER stress induced by tunicamycin and thapsigargin activates the **ISR** at 16h

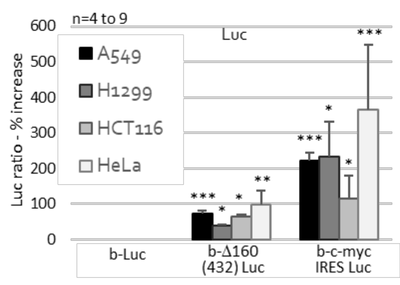
↓

The levels of **Δ160** and **Δ133** are strongly increased

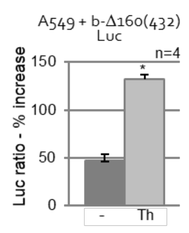
2. The internal translation initiation of Δ160p53



Bicistronic dual-luciferase constructs:
Translation of *Renilla* luciferase is cap-dependent, while the translation of *Firefly* luciferase depends on internal initiation mediated by the mRNA region upstream; the hairpin prevents reinitiation from the first cistron.

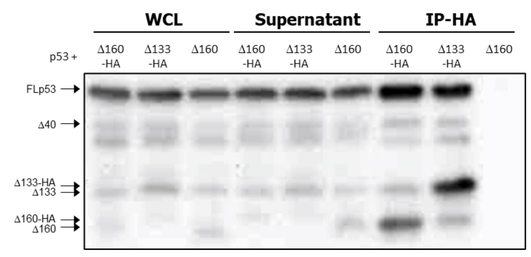


A region of Δ160 RNA exhibits **IRES** activity



Internal translation of Δ160 is stimulated by the **ISR**

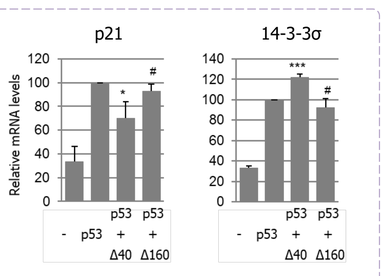
3. Δ160p53 and Δ133p53 interact with FLp53



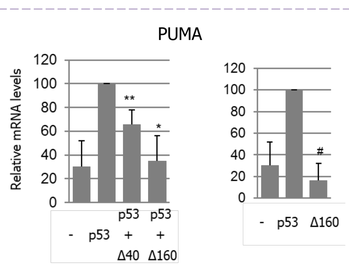
Cell line: H1299 (p53-null lung carcinoma)

Affinity for FLp53:
Δ160 > Δ133

4. Δ160p53 modulates the transcriptional activity of FLp53

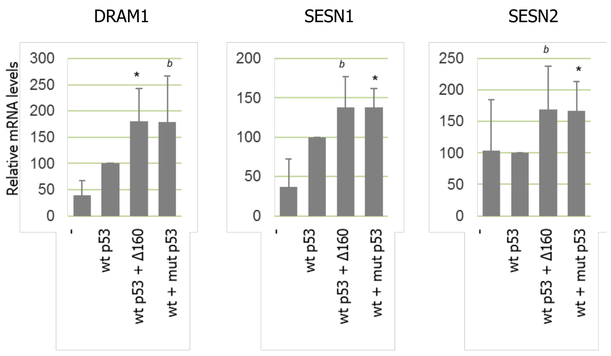


Δ160 has no effect on the expression of **p21** (G1 arrest) or **14-3-3σ** (G2 arrest)



Δ160 strongly inhibits FLp53-mediated activation of **PUMA**, a pro-apoptotic gene, but shows no effect in the absence of FLp53

p53 target genes enhanced in cancer cells



The R248Q p53 mutant (mut) favors the activation of **SESN1/2** and **DRAM1** by FLp53 (wt), but Δ160 matches its effect

SESN1/2 and **DRAM1** are known p53 target genes involved in autophagy;

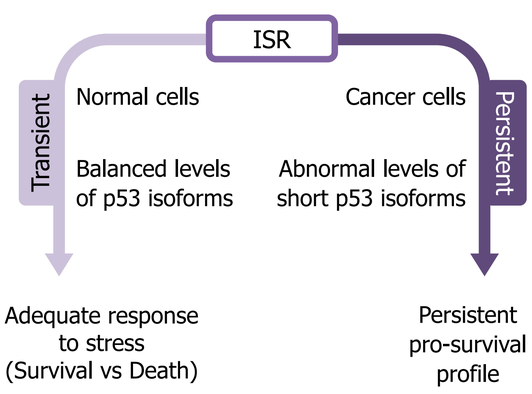
Increased levels of these genes were identified in a study in breast cancer;

Autophagy is activated in response to stress to promote cell survival.

Shown are averages ± s.d. of n=3 experiments; #$P > 0.1$, $^{b}P < 0.1$ *$P < 0.05$, **$P < 0.01$ and ***$P < 0.005$ compared to p53 alone

Conclusions

- The p53 short isoforms Δ133 and Δ160 are activated by the ISR in response to stress;
- Δ160 binds FLp53 with a strong affinity and modulates its target gene specificity;



- The oncoprotein inside TP53 is released during ISR to balance the role of p53 in restoring homeostasis;
- This intersection uncovered between p53 isoforms and ISR could open a new path for future cancer therapies.

References

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Or send an e-mail to:
a.catarina.ramalho@insa.min-saude.pt

This research was funded by grants 18K07229 (KAKENHI) from Japan Society for the Promotion of Science (JSPS) and PTDC/MED-ONC/32048/2017 from Fundação para a Ciência e a Tecnologia of Portugal (FCT). This work was supported by FCT through the individual research grant 2020.06982.BD.