Molecular Influence of the ATM Protein in the Treatment of Human Cells with Different Radioprotective Drugs: Comparisons between Antioxidative and Pro-Episkevic Strategies

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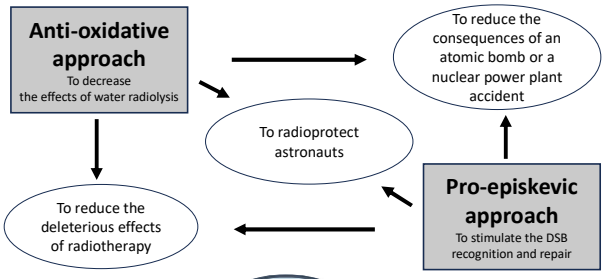
Challenge : Development of a new approach for radiation protection and radiation mitigation

Anti-oxidative approach :

- Historical applications
- To decrease DNA damage
- N-acetylcysteine (NAC), amifostine
- Applied in radiotherapy



Pro-episkevic approach :

- To stimulate Double-Strand Breaks (DSB) repair
- Statins (pravastatin), bisphophonates (zoledronate)

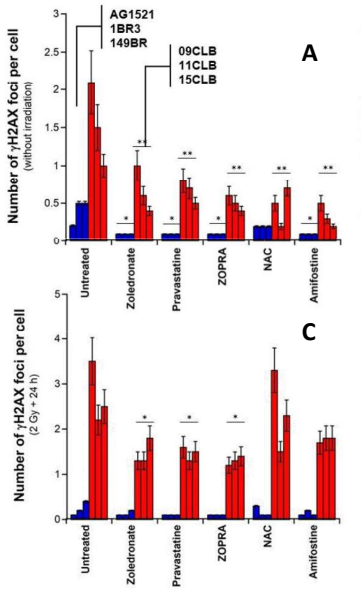
Hypothesis

Applying a pro-episkevic strategy involving the concurrent administration of statins and bisphosphonates has the potential to enhance the efficacy of DSB recognition and repair mechanisms, rendering it a more effective approach for radioprotection.

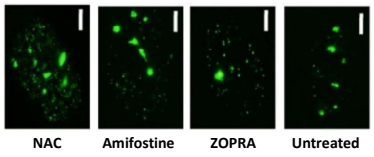
Methods

- Different radioresistant and radiosensitive skin fibroblasts irradiated with 2 Gy of 6 MeV X-rays.
- Different conditions: pretreated or not with amifotine, NAC, zoledronate and/or pravastatine (ZOPRA).
- Immunofluorescence from 10 min to 24 h post irradiation with DSB biomarkers γH2AX and pATM.

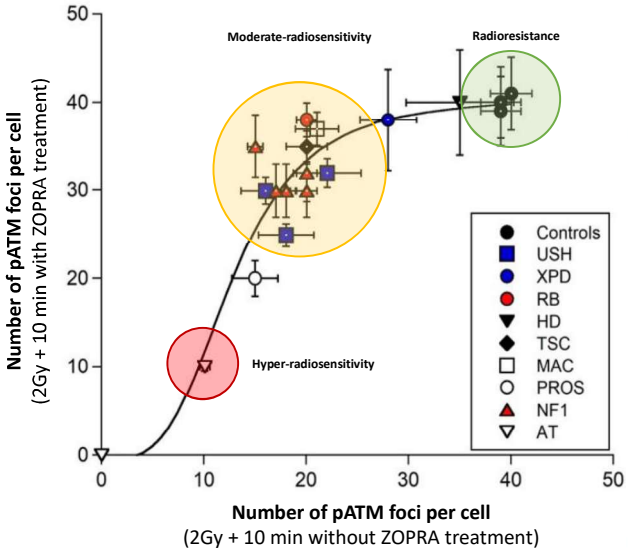
Results



Radioprotective effect of a pretreatment. Number of γH2AX foci per cell assessed for each indicated pretreatment before irradiation (A), followed by 2 Gy X-rays irradiation and 10 min (B) or 24h (C) incubation.
In blue: radioresistant fibroblasts cell lines, in red: radiosensitive cell lines.

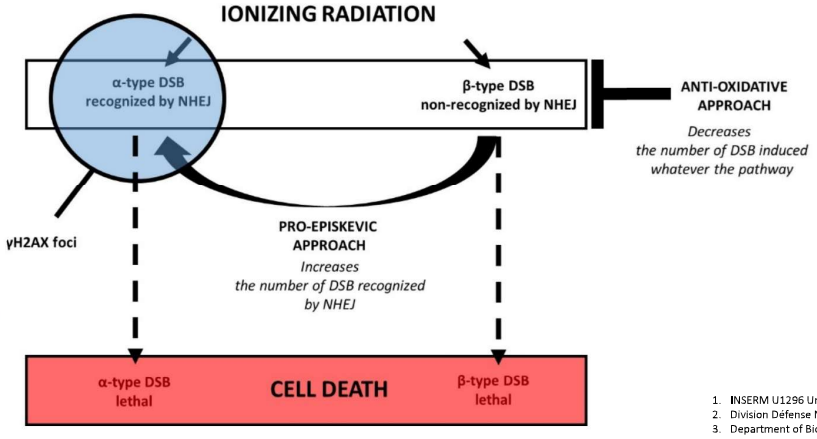


Representative examples of γH2AX foci, in untreated, NAC-, Amifostine-, ZOPRA- pretreated 09CLB radiosensitive cells.



Radioprotective effect of ZOPRA in fibroblasts derived from 10 radiosensitive genetic syndromes with pATM foci. The number of pATM foci assessed at 10 min post irradiation (X-rays) with and without ZOPRA pretreatment were plotted together. Usher's syndrome (USH), PROS syndrome (PROS), McCune-Albright syndrome (MAC), retinoblastoma (RB), Tuberous Sclerosis Complex syndrome (TSC), Huntington Disease (HD), Xeroderma pigmentosum D (XPD), Neurofibromatosis 1 (NF1), LIG4 syndrome (LIG4) and Ataxia Telangectasia (AT).

Conclusions



Comparison of two different approaches :

- Antioxidant approach : the number of all DSB, recognized (α -type) or not recognized (β-type) by efficient repair pathways, is decreased.
- Pro-episkevic approach: the stimulation of efficient repair pathways, reflected by an increased of the number of DSB recognized (α -type) and a decrease of the number of DSB non-recognised (β-type) .

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