Modulation of TGF-β Expression by Metformin in X-Ray-Irradiated Human Skin

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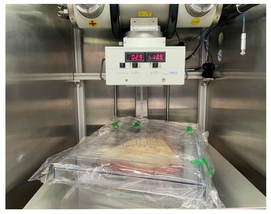
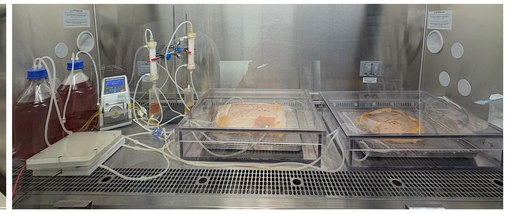
INTRODUCTION

Transforming growth factor-beta (TGF-β) plays a critical role in tissue remodeling and fibrosis following radiation exposure. Elevated TGF-β levels post-irradiation contribute to excessive collagen deposition, tissue stiffening, and impaired wound healing, ultimately leading to fibrosis. Targeting TGF-β expression offers a potential therapeutic strategy for preventing fibrotic complications in irradiated skin. Metformin, a widely used anti-diabetic drug, has demonstrated anti-fibrotic properties in various tissues by downregulating TGF-β signaling.

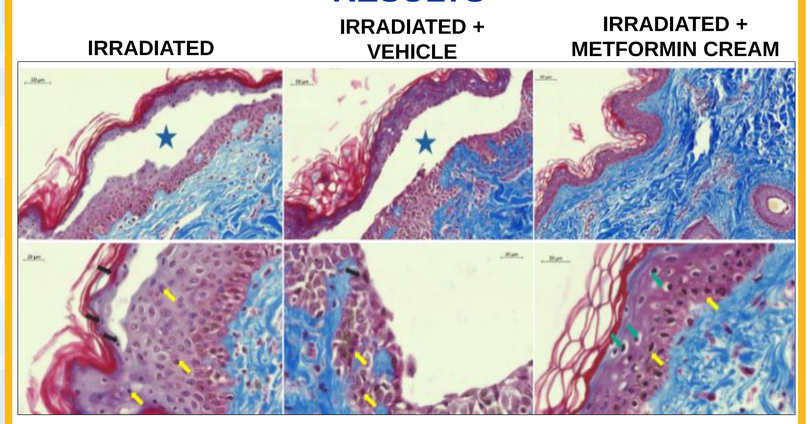
MATERIALS & METHODS

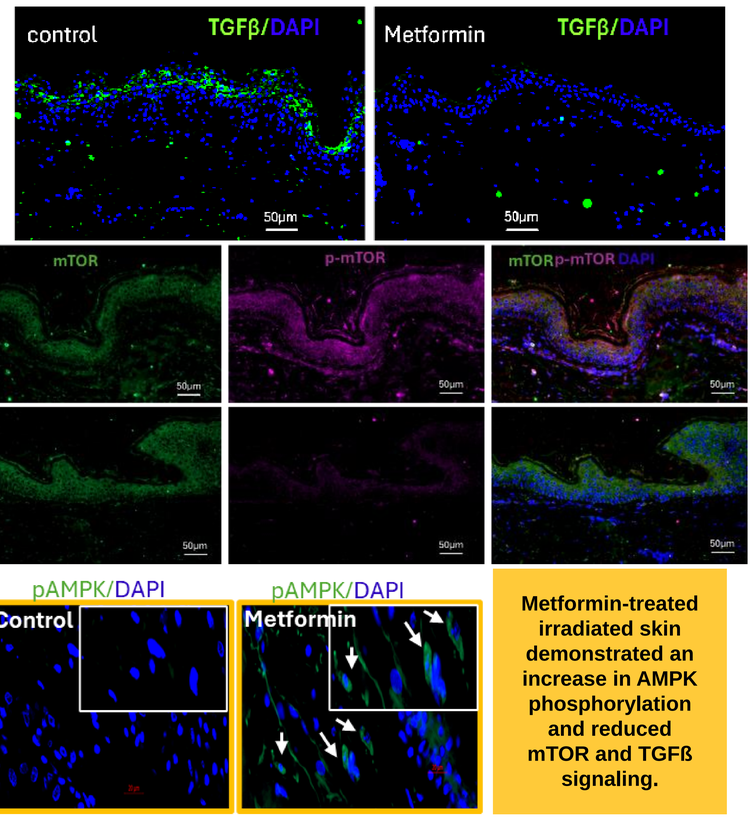
In this study, we evaluated the ability of topical metformin to modulate TGF-β expression in human skin following X-ray irradiation. Skin flaps maintained on an ex vivo perfusion system were exposed to 10 Gy of X-ray radiation and divided into three groups: irradiation only, irradiation with a control cream, and irradiation with metformin cream. Biopsies were collected at days 2, 7, 11, and 13, and TGF-β expression was assessed through immunohistochemistry.



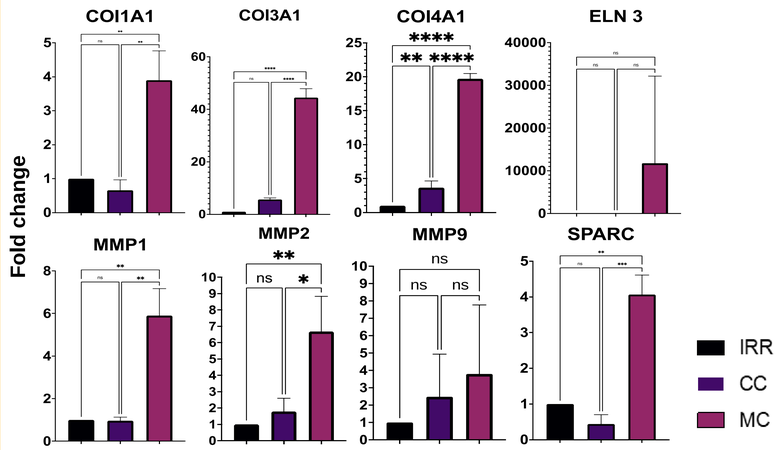


RESULTS





Metformin-treated irradiated skin demonstrated an increase in AMPK phosphorylation and reduced mTOR and TGFß signaling.



Metformin-treated skin showed decreased TGF-β expression, improved tissue architecture, and reduced collagen deposition, highlighting its ability to attenuate radiation-induced fibrosis.

RESULTS

- Masson's Trichrome staining demonstrated conservation of intact epidermis from day 1 to day 13, in irradiation + metformin-treated group, in comparison to irradiated and irradiated + control cream groups.
- Metformin-treated skin displayed a decrease in TGF-β levels compared to untreated irradiated skin, with the most substantial reductions observed at days 11 and 13 post-irradiation.
- The reduction in TGF-β expression correlated with enhanced tissue structure and organization, indicating better preservation of skin integrity.
- Q-PCR analysis also demonstrated a significant upregulation of ECM remodeling markers (*COL1A1, COL3A1, COL4A1LELB3,MMP1,MMP2,MMP9,SPARC*) in metformin-treated group in comparison to non-treated groups.
- The findings suggest that metformin effectively prevents radiation-induced fibrotic changes by modulating TGF-β signaling pathways.

CONCLUSIONS

- Metformin demonstrates potential as a topical therapeutic agent for preventing radiation-induced fibrosis by downregulating TGF-β expression.
- By reducing TGF-β levels, metformin minimizes collagen deposition and supports tissue integrity, offering protection against fibrotic changes in irradiated skin.
- These findings provide evidence for metformin as a novel strategy to manage fibrotic complications in skin exposed to radiation.
- Metformin could be utilized in radiotherapy patients or individuals exposed to radiation accidents to safeguard skin health and prevent fibrosis.

Metformin's properties make it a promising therapeutic agent to mitigate radiation-induced damage and to enhance tissue repair and regeneration