Novel protective effect of prostaglandin for timely hair follicle regeneration from radiation injury

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Purpose

Tissue stem cells are often responsible for regeneration after injury. The highly proliferative hair follicles (HFs) are one of the organs that are sensitive to radiation and hair loss is a common side effect that still lacks an effective treatment. Due to the quiescent nature of bulge stem cells in HFs, their activation requires considerable time and signaling relays to reset hair cycles. Treatment that can fasten the regenerative process will help to shorten the downtime before functional recovery. In this work, we try to characterize the novel effect of prostaglandin, which may help for timely regeneration of HFs following radiation injury.

Methods

Single dose of gamma irradiation (8.5Gy) were given to C57BL/6 mice in the early full anagen(growth phase). A single dose of dmPGE$_2$ (A stabilized derivative of prostaglandin E2, 16,16-dimethyl-PGE$_2$) is given locally at 2hr before irradiation. Skin samples will be harvested at the indicated time points following irradiation for histological analysis. The gross appearance of hair was serially recorded. The dynamics at different time points was analyzed by histology, immunohistochemical analysis and lineage tracing. Cell behavior was modulated by pharmacological and genetic tools in vivo.

Results

We observed that local prostaglandin E2 (PGE$_2$) pretreatment could reduce hair loss from radiation injury by preventing entry into catagen (regression phase) and telogen (resting phase) (**Figure1**). Surprisingly, quiescent hair follicle bulge stem cells were not activated. Instead, the dystrophy of hair bulbs where hair follicle transit amplifying cells (TACs) reside was reduced and concentric layers of anagen hair follicle structures were quickly regenerated. The proliferation of TACs was halted by PGE$_2$ pretreatment and immunostaining of cell cycle markers suggesting PGE$_2$ might reduce the radiosensitivity of TACs through cell cycle modulation.

(Unirradiated)   (Irradiated)   (Irradiated with PGE2 pretreatment)
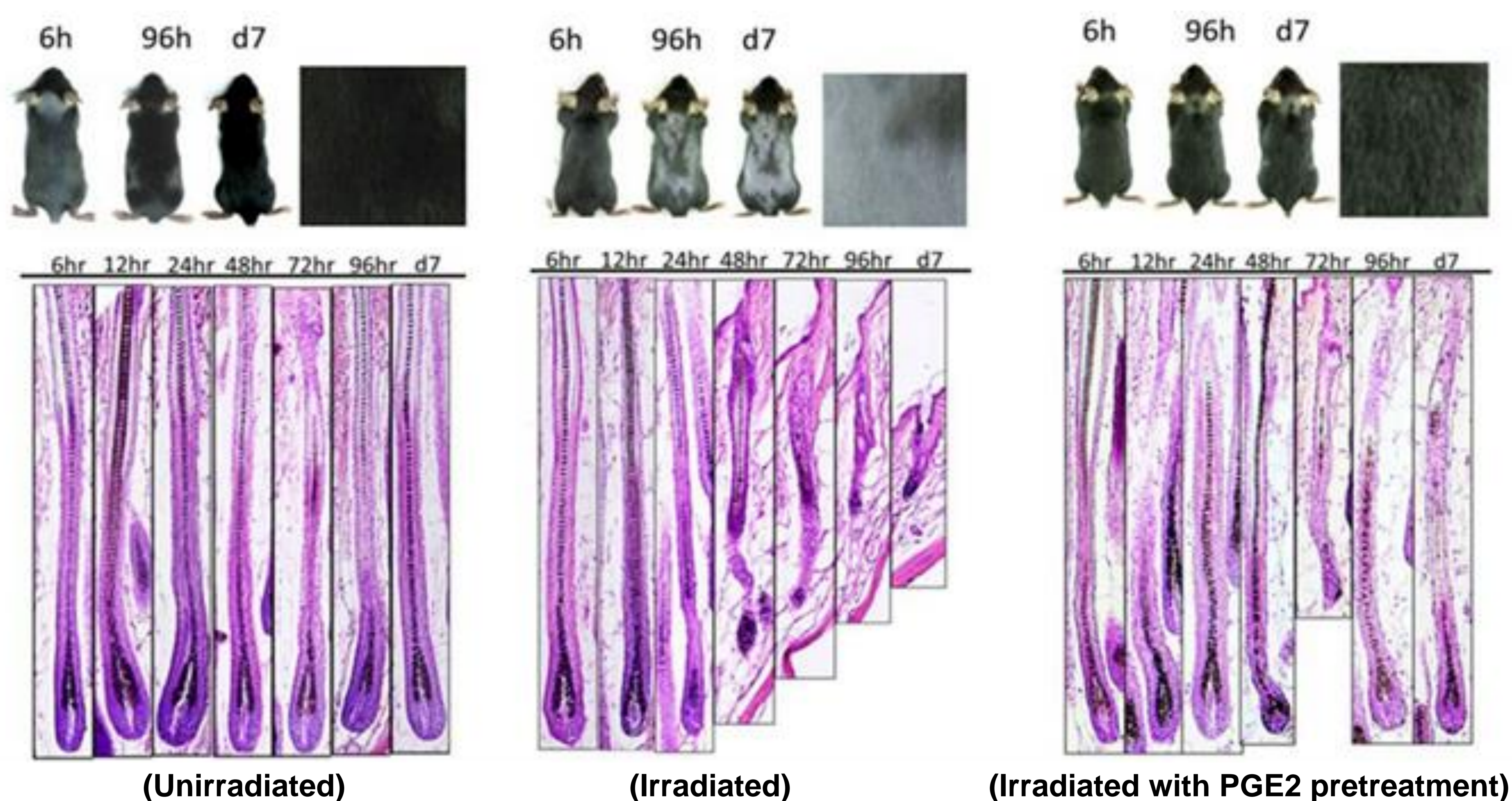
Figure 1. Effect of local PGE$_2$ pretreatment and radiation on anagen follicle.
Histology of serial changes of HF was examined by H&E staining. 8.5Gy of IR injury resulted in the severely dystrophic change of HFs with the induction of premature catagen followed by progressive shrinkage into telogen from 6hrs to day 7, which caused severed hair loss. In contrast, with local dmPGE$_2$ pretreatment, HFs progressively shrank to a slender epithelial strand of about one third of the length of an anagen HF at 72hrs followed by restoration of the anagen HF morphology and length from 96hrs to day 7, thus, the architecture of anagen HFs was rescued by PGE$_2$ and IR-induced hair loss was not observed.

Conclusions

Under radiation injury, local PGE2 pretreatment might protect hair follicle TACs against radiation injury through modulating their cell cycles and the preserved TACs can serve as "reserve stem cells" to regenerate the lost structures to resume anagen growth, thus bypassing the long downtime needed to rest hair cycles through telogen for bulge stem cell activation.