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Radiation-induced skin fibrosis: pathogenesis, current treatment options, and emerging therapeutics

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Abstract

Radiotherapy (RT) has become an indispensable part of oncologic treatment protocols for a range of malignancies. However, a serious side effect of RT is radiodermatitis; almost 95% of patients develop moderate to severe skin reactions following radiation treatment. In the acute setting, these can erythema, desquamation, ulceration, and pain. Chronically, soft tissue atrophy, alopecia, and stiffness can be noted. Radiodermatitis can delay oncologic treatment protocols and significantly impair quality of life. There is currently a paucity of effective treatment options and prevention strategies for radiodermatitis. Importantly, recent preclinical and clinical studies have suggested that fat grafting may be of therapeutic benefit, reversing detrimental changes to soft tissue following radiation therapy. This review outlines the damaging effects of RT on the skin and soft tissue as well as discusses currently available treatment options for radiodermatitis. Emerging strategies to mitigate detrimental, chronic radiation-induced changes are also presented.

Introduction

Radiation therapy or radiotherapy (RT) has become an essential part of curative as well as palliative oncologic treatment protocols for a range of malignancies; currently RT is used as an adjunct therapy in over 50% of cancer patients^{1,2}. While delivery methods for RT have been developed to combat cancer more effectively, collateral damage to healthy tissue in the radiation field surrounding the area of malignancy remains a serious adverse outcome. Skin is particularly radiosensitive, and over 95% of patients receiving RT develop moderate to severe skin reactions^{3,4}. In the acute phase following radiation exposure, the skin typically becomes erythematous and may desquamate or ulcerate. On the molecular level, cytokine cascades and fibro-inflammatory pathways are up-regulated due to radiation which can

progress for many years leading to substantial fibrosis, the hallmark of chronic RT damage⁵. Cutaneous fibrosis alters form, function, and aesthetic appearance of the skin, and the consequences can significantly impact quality of life. Although a number of treatment options have been described, none has proven to be effective in preventing or reversing radiation-induced fibrosis (RIF) of the skin. Recent clinical and preclinical studies have demonstrated the benefit of autologous fat grafting (AFG) in the treatment of RIF^{6,7}. First used for reconstructive purposes, fat is increasingly recognized to exert regenerative effects upon the tissue into which it is transplanted^{8–10}. In irradiated skin, fat grafts can attenuate acute inflammation and slow/reverse the progression of chronic RIF⁶. The mechanisms by which fat regenerates the overlying skin and soft tissue remains to be elucidated but is thought to be driven by the adipose derived stromal cells (ASCs) of the stromal vascular fraction (SVF) of adipose tissue. ASCs have potent paracrine signaling action and are also multipotent and able to differentiate into a number of mesenchymal cell lineages. In this review, we outline the current understanding of RIF, the current treatment options, and the benefit of AFG within this setting. We also delve into alternative emerging strategies to mitigate RIF.

Radiation-induced cell death

Radiation therapy is the process of delivering lethal doses of radiation to areas of malignancy to kill cancer cells. Radiation therapy has evolved to allow for more specific targeting of cancer cells and reduction of the “bystander response” in neighboring healthy tissue¹¹. There are three main ways to deliver RT: 1) *External beam radiation therapy* directs radiation beams from outside of a patient’s body in the direction of the tumor; 2) *Brachytherapy* delivers radiation internally with the insertion of radioactive materials inside the body; and 3) *Radioisotope therapy* systemically circulates radiation throughout the bloodstream via injection of a targeted radioisotope^{12–14} RT can utilized alone or can be combined with other treatment modalities—such as chemotherapy or surgery—to treat primary malignancies as well as metastatic disease¹⁵.

Radiation therapy is based on the concept that malignant cells are more sensitive to radiation and cannot repair damage as efficiently as healthy cells. The molecular mechanisms of radiation-induced cell death are not completely understood¹⁶, and several mechanisms may be at play. Within hours of radiation, a number of cytokine signaling and inflammatory cascades are initiated. Radiation therapy forms ions that pass through tissues which can directly induce double-stranded breaks in genetic material¹⁷. Cell death ensues via apoptosis, mitotic cell death, necrosis, and/or senescence¹² including the release of damage-associated molecule pattern (DAMP) molecules^{18,19}. Release of DAMPs activates the innate and adaptive immune systems that allows for additional antitumor responses^{20,21}. Energy from ionizing radiation also acts on other molecules within cells, such as water, to generate reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radical, which indirectly cause further damage of the DNA and other cellular components (e.g. proteins, lipids)^{22,23}. Generation of ROS are thought to account for more than 60% of the total radiation induced damage^{24,25}.

To improve targeting of malignant cells with radiation therapy, Begg and colleagues have described several approaches to modulate cellular response to radiation. These include inhibiting additional DNA repair mechanisms, cell cycle checkpoints, and signal transduction pathways²⁶. For example, breast cancer cells with BRCA1 or BRCA2 mutations already have an impaired ability to repair double-stranded breaks in DNA via homologous recombination and rely on other mechanisms of DNA repair, such as base excision repair and single-strand break repair, to survive²⁶. Farmer et al. found that exposure of BRCA1- or BRCA2-deficient embryonic stem cells to an inhibitor of poly(ADP-ribose) polymerase—an enzyme involved in base excision repair—resulted in cell cycle arrest and apoptosis²⁷. Inhibition of alternative survival and signaling pathways would thus render cancer cells more vulnerable to radiation-induced DNA damage while sparing normal cells that retain other mechanisms of repair.

Radiodermatitis

While it is the aim of RT to deliver sufficient levels of radiation to induce death of cancer cells, damaging effects on surrounding healthy cells should be minimized. Substantial progress has been made towards this goal, but damage to healthy soft tissue within the radiation field remains a significant problem. The proliferative nature, high oxygen requirement, and superficial nature of the skin make it the most frequently damaged tissue following RT^{28,29}. Collectively, damage to the skin following RT is known as radiodermatitis and is typically categorized into acute and chronic stages. In the early phase following radiation exposure, the skin appears discolored, erythematous, and inflamed. Severely damaged skin may desquamate, atrophy and/or ulcerate^{30–32}. The chronic phase of radiation damage is marked by radiation-induced fibrosis—the final common pathology across multiple tissue types. Skin RIF involves substantial dermal and epidermal induration, scarring and retraction, with histological evidence of extensive hyalinization of reticular collagen. There may be associated permanent scarring alopecia or loss of hair pigmentation^{33–38}, suggesting an irreversible loss of hair follicle stem cells and melanocyte stem cells. The epidermis may be hyperplastic or atrophic and develop chronic ulcers and/or skin tumors.^{39,40} Chronic radiation-induced fibrosis typically develops within 4 to 12 months after therapy but may continue for many years in a progressive fashion⁴⁰.

The same mechanisms at play in killing cancer cells are also responsible for causing radiodermatitis (Fig. 1). Immediately following exposure there is an inflammatory response, and neutrophils are attracted to the site of irradiation by cytokines that are released by damaged skin and endothelial cells. Upon entry to the irradiated area, neutrophils are stimulated further and release pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, and IL-6, which perpetuate inflammation and increase formation of ROS. Monocytes and lymphocytes subsequently migrate to irradiated skin. Upon entry into irradiated tissue, monocytes differentiate into macrophages, and release platelet-derived growth factor (PDGF) which stimulates angiogenesis and the migration of fibroblasts⁴¹. Finally, macrophages, along with the native endothelial cells, fibroblasts, and epidermal cells, secrete transforming growth factor-beta (TGF- β)^{5,42}, a potent pro-fibrotic factor which is elevated in the early phases of radiation damage⁵ and heavily implicated in the pathogenesis of RIF. TGF- β binds the TGF β RI receptor and thus induces phosphorylation,

and activation of the intracellular receptor-associated Smads (R-Smads). Activated R-Smads form heteromeric complexes with a co-Smad (Smad4), translocate to the nucleus, and induce pro-fibrotic gene transcription, either by directly binding DNA or by associating with other transcription factors^{43–45}.

TGF- β activates a number of pro-fibrotic pathways that drive the pathogenesis of radiodermatitis. Following radiation, TGF- β stimulates the differentiation of fibroblasts into myofibroblasts⁴⁶, which in turn secrete excessive amounts of ECM proteins including collagen, fibronectin, and proteoglycans⁴⁷. Increased ECM production is further compounded by impaired matrix degradation. TGF- β decreases the activity of matrix metalloproteinase (MMP) activity, specifically MMP-2, MMP-9, and MMP-1, within fibroblasts^{30,31,48}. Consequently, there is net gain of ECM that amounts to increased tissue stiffness and thickness, characteristic of chronic RIF. TGF- β in radiation also activates the process of epithelial to mesenchymal transition (EMT) and the interferon (IFN)- γ response⁴⁹ which can also contribute to soft tissue fibrosis. Chronic activation of many of these fibrotic pathways is thought to persist for years after initial exposure. Indeed, elevated levels of collagen type I, collagen type III, and TGF β 1 are detectable in breast biopsies even 20 years post-radiotherapy⁵.

The fibrotic changes in skin are also accompanied by damage to the vasculature. Histologically there is evidence of decreased microvascular network density and alterations to the morphology of blood vessels⁵⁰. Acutely following radiation exposure, the vessels of mice become plugged with fibrin and leukocytes, with evidence of endothelial swelling and hyperplasia and perivascular fibrosis.^{46,51} These changes decrease blood supply to the tissue and lower oxygen tension, which further stimulates fibrosis by increasing expression of collagen type 1 alpha 1 (COL1A1)⁵².

The consequences of RIF are profound, and up to 30% of patients that receive RT to the breast or chest wall experience severe RIF^{53–58}. RIF reduces tissue perfusion and further worsens the quality and function of the irradiated skin⁵⁰. Tissue fibrosis can disrupt lymphatic and vascular drainage, which produces hypoxia and predisposes to ulceration and impaired wound healing^{59,60}. This often results in severe soft tissue defects that may require coverage with vascularized tissue. Furthermore, implant-based breast reconstructions in the irradiated setting show significantly higher complication rates such as capsular contracture or infection necessitating implant removal or replacement⁶¹. As increasing numbers of individuals are surviving cancer, more patients are living with the long-term effects of radiation treatment⁶². Radiation-induced fibrosis is therefore especially undesirable for patients with malignancies where treatment can be curative⁶³.

Current treatment options

Although some therapies have been shown to delay the onset or reduce the risk of developing RIF, a key step of prevention is to minimize radiation doses to areas of exposed healthy skin. Current treatment options, while limited, range from physical therapy to oral and topical medications. Recent advances in surgical treatment options with autologous fat

grafting have also been reported, with some success noted in reversing detrimental changes seen in chronically damaged skin and soft tissue⁶⁴.

Physical therapy with massage is a non-medical option that, in two studies, has been shown to have some promising results. In one study, twenty patients who had been treated for breast cancer with surgery and radiotherapy were enrolled in a randomized control trial that assessed mechanical massage compared with medical observation alone. Mechanical massage was found to be superior at reducing erythema, pain, pruritus, skin induration, and skin softening⁶⁵. In a second study, deep friction massage was found to reduce RT-associated muscle spasms, though it did not have any effect on skin appearance⁶⁶. Massage may have the potential to break down fibrotic tissues, particularly in the thoracic region following breast cancer radiation therapy, interrupting the progressive nature of radiation-induced fibrosis. However, larger, more rigorous studies have yet to be performed to confirm these findings.

Antioxidants have also been studied for their preventative and therapeutic effects in protecting healthy cells from radiation-induced DNA damage⁶⁷. Silymarin, an extract from milk thistle with antioxidant and anti-inflammatory effects, was noted to delay the onset of radiodermatitis in a randomized trial of forty breast cancer patients when applied topically as a gel for five weeks at the onset of RT⁶⁸. In a prospective, nonrandomized study of 112 patients post-mastectomy, daily subcutaneous administration of the antioxidant amifostine throughout radiation treatment was associated with reduced erythema, edema, and moist skin desquamation compared with patients who did not receive antioxidant treatment⁶⁸. Finally, the hemorrhheologic agent pentoxifylline has also been shown to have antioxidant effects. Along with improving blood flow, this medication may also inhibit fibroblast proliferation and has been shown to both prevent and treat RIF⁶⁹. Randomized control trials have shown that the combination of oral pentoxifylline with alpha-tocopherol (vitamin E) improves tissue compliance in breast cancer patients when taken daily for six months post-RT and reduces the RIF surface area even when administered years after RT for breast or head and neck cancer^{70,71}. However, recent studies have found compliance with pentoxifylline and vitamin E therapy to be poor in almost 40% of patients, with nausea the most frequently reported indication for treatment dose reduction or discontinuation of therapy⁷².

Topical treatments including steroids, gels, and creams have also been studied extensively in randomized trials for treatment of radiation-induced fibrosis. Use of a topical corticosteroid (0.1% methylprednisolone) in concert with 0.5% dexpanthenol, a derivative of pantothenic acid which is an essential component of normally functioning epithelium, delayed the emergence of clinical and functional symptoms of radiation dermatitis by one week in 15 breast cancer patients compared with untreated controls.⁷³ Similarly, a randomized trial of 51 breast cancer patients revealed that topical 0.1% betamethasone delayed, but did not prevent, the occurrence of radiation dermatitis⁷⁴. Daily use of topical 0.1% mometasone furoate reduced symptoms of radiation-induced skin toxicity, which included assessments of pruritus, irritation, and burning, compared with placebo cream in 176 patients treated with breast or chest wall RT⁷⁵. Furthermore, creams containing hyaluronic acid or urea may delay or reduce the severity of RT-induced skin effects. In a prospective observational study, 98

breast cancer patients received treatment with lotion containing 3% urea, polidocanol, and hyaluronic acid two to three weeks prior to starting RT. Fewer developed radiodermatitis and of those that did, skin toxicity was reduced compared with controls who did not receive the lotion⁷⁶. Finally, in a randomized, double-blind, placebo-controlled study, 152 patients with head and neck, breast, or pelvic cancer who received treatment with hyaluronic acid cream for six weeks had delayed and reduced skin reactions to the radiation therapy⁷⁷.

Fat grafting

The challenges presented by the treatment of RIF have popularized the view that RIF is irreversible. Recently, this concept has been questioned with increasing attention turned to autologous fat grafting and its ability to improve post-irradiated, fibrotic skin^{7,78}. Originally used for volume restoration in reconstructive surgery, fat has become increasingly recognized for its ability to regenerate damaged tissue^{7,50,79,80}. Autologous fat grafting has also been reported to potentially antagonize the effects of aging⁸⁻¹⁰. In 2007, Rigotti and colleagues⁷ first demonstrated that fat grafting resulted in visible and symptomatic improvements in 20 patients with RIF following previous radiation treatment for breast cancer. One year after grafting, tissue biopsies showed well vascularized tissue and evidence of fibrosis regression. Since this landmark finding, AFG has been used by more surgeons to reconstruct previously irradiated tissue^{8,50,81-83}. Salgarello et al. reported that fat grafting reduced the radiation-related complications in two patients undergoing breast reconstruction⁷⁹, and subsequently in a retrospective review of 16 patients⁸⁴. In a large prospective clinical study, 65 previously irradiated post-mastectomy patients received tissue expanders and AFG as part of their breast reconstruction. With this approach, patients were found to have improved skin quality of the reconstructed breast with reduced capsular contracture (Baker grade 1) at 6 months, and this was accompanied by high patient and surgeon satisfaction⁸⁵. Similarly, Phulpin et al. reported functional and aesthetic benefits in 10 out of 11 patients in whom AFG was used for head and neck reconstruction after RT. Specifically, patients had improved phonation, swallowing, and breathing, with histologic evidence of increased vascularization and normal tissue composition without areas of necrosis⁵⁰. These reports have been supported by multiple preclinical studies, showing that fat grafting in the irradiated mouse decreases disordered collagen content and thickening of the overlying dermis⁶, and can increase skin perfusion, as measured by Laser Doppler and immunofluorescence staining⁵¹.

While the mechanisms driving these beneficial clinical findings with AFG remain to be elucidated, it is believed that cells within the SVF of adipose tissue, in particular the ASCs, are largely responsible. Adipose tissue is rich in ASCs, which possess multi-lineage potential and the ability to release potent proangiogenic and anti-apoptotic growth factors^{8,86,87}. ASCs may promote angiogenesis by releasing pro-angiogenic growth factors in the recipient site. Consistent with this hypothesis, grafted fat in the irradiated skin of mice was found to increase expression of pro-angiogenic growth factors, such as vascular endothelial growth factor and stromal cell-derived factor 1, and decrease expression of COL1A1 and TGF β ⁵¹. Alternatively, ASCs may directly differentiate along various mesenchymal lineages forming endothelial cells which can integrate themselves into newly formed vessels⁸⁸. Interestingly, a recent study performed whole genome expression analyses

on human adipose tissue biopsies harvested from the irradiated and non-irradiated breasts of 10 patients before and 1-year after AFG⁴⁹. The results indicated that RT causes dysregulated expression of fibrosis-related pathways in human adipose tissue including two canonical pathways: interferon- γ response and hypoxia response. Macrophages were also recruited to the irradiated tissue. Importantly, the dysregulated genes returned to nearly normal expression levels following AFG, supporting the use of AFG in the use of RIF.

Overcoming the challenges of fat-grafting in irradiated tissue

Though fat grafting has shown incredible promise with treatment of radiation-induced soft tissue injury, there remains a number of challenges to address, particularly with grafting into hostile irradiated tissue. Fat retention is already variable even at non-irradiated recipient sites, and resorption rates may range between 40 and 60%^{89,90}. Delivery of small aliquots of adipose tissue into well-vascularized sites can increase survival⁹¹⁻⁹³, but irradiated tissue is hypovascular, inflamed, and fibrotic^{51,78}. This can lead to fat necrosis and stimulate an inflammatory reaction resulting in fibrosis, cyst formation, calcification, or local infection⁹⁴⁻⁹⁷. When used for breast reconstruction, AFG has been reported to show increased rates of fat necrosis and infection in the irradiated compared to non-irradiated breast^{79,98,99}. However, several strategies have been recently developed to help overcome some of the limitations of fat-grafting into irradiated tissue as related to the processing of harvested fat and preconditioning of the recipient site.

A variant of fat grafting called cell-assisted lipotransfer (CAL) involves the enrichment of fat graft with cells from the SVF or with culture-expanded ASCs. CAL has been clinically shown to have improved fat retention and cosmetic outcomes¹⁰⁰⁻¹⁰². In support of this, recent animal studies have also reported improvement in histologic metrics of fat, as well as decreased dermal thickness, improved structural quality, and greater vascularization with supplemented compared to non-supplemented grafts⁷⁸. Furthermore, CAL was found to significantly improve stiffness of irradiated mouse skin when compared unenriched fat grafts alone. However, while these results are promising, ASCs are increasingly recognized to be a heterogeneous mix of cells comprised of multiple subpopulations with distinct functions. For example, BMPR-1A⁺ ASCs have enhanced capacity for adipogenesis¹⁰³, CD248⁺ ASCs have augmented angiogenic potential¹⁰⁴, and CD105- (endoglin) have enhanced osteogenic capacity¹⁰⁵. Future outcomes of fat grafting, especially in the irradiated setting, may thus be potentially enhanced by enrichment for specific subpopulations with increased angiogenic, adipogenic, or antifibrotic qualities.

Fat survival may also be increased by improving the quality of the recipient site prior to transplantation. Deferoxamine (DFO) is an iron chelator that has been FDA-approved for use in iron overload syndrome. This chelating action, however, also stabilizes and thus increases hypoxia-inducible factor-1 alpha which can induce the local expression of angiogenic growth factors^{106,107}. Furthermore, DFO has been shown to possess antioxidant properties, and topical application has been found to reduce reactive oxygen species within the skin¹⁰⁶. These properties are thought to mediate the improved vascularization of ischemic wound flaps and enhance wound healing in mice treated with DFO^{108,109}. Deferoxamine may thus also be of benefit in promoting vascularization and reducing ROS-

mediated cellular injury following radiation therapy. Indeed, local administration of DFO into irradiated mouse skin has been found to enhance vascularization and subsequent fat graft retention while also reducing dermal thickness¹¹⁰. Furthermore, transdermal delivery of DFO to irradiated rat skin has been shown to reduce collagen fibril disorganization by atomic force microscopy¹¹¹. These findings highlight an emerging strategy with DFO to mitigate, and possibly prevent, the debilitating soft tissue changes associated with radiation therapy.

Conclusions

Over 1.5 million new cancer cases are diagnosed every year¹¹², and over half of these patients will receive RT. While RT is immensely beneficial, an enhanced understanding of the mechanisms of RIF-induced changes is essential for the development of effective strategies to prevent long-term disability and discomfort following radiation therapy. This has led to emerging strategies including autologous fat grafting and deferoxamine which hold great promise for improving the quality of life in patients suffering from the debilitating sequelae of radiation treatment.

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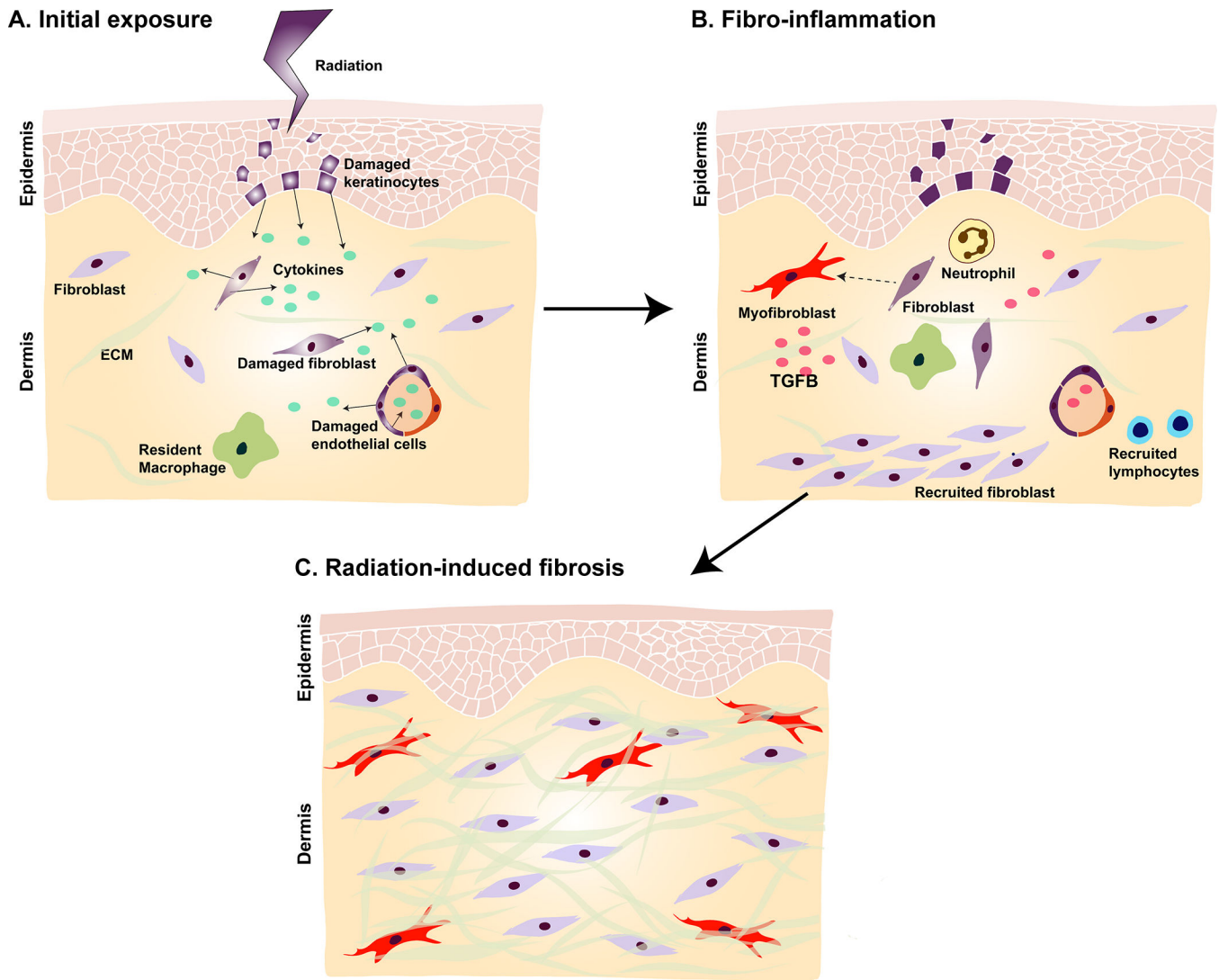


Fig. 1. The proposed mechanism underlying radiation-induced fibrosis (RIF).

A) RT delivers ions that directly induces DNA damage and generates reactive oxygen species (ROS). Damaged cells in the skin and endothelium (colored purple) release cytokines, leading to activation of the innate and adaptive immune systems and recruitment of inflammatory cells. **B)** Once recruited to the irradiated area, neutrophils release additional inflammatory mediators to sustain inflammation. Lymphocytes and monocytes also migrate to the location of injury, the latter of which differentiate into macrophages. Macrophages, fibroblasts, native endothelial cells, and epidermal cells release transforming growth factor-beta (TGF- β) which stimulates fibroblasts to differentiate into myofibroblasts. **C)** Myofibroblasts secrete excess amounts of extracellular matrix proteins, leading to increased tissue stiffness and thickness. Over time, RIF ensues and may persist even decades after radiation therapy.