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Topical Fibronectin - Novel Therapeutic Approach Has Been Formulated for Radiation Induced Skin Reactions

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ABSTRACT

For a long time, radiation-induced skin reactions (RISR) or radiation ulcer (RU) were only encountered in patients undergoing radiation therapy. Nearly 90% of patients having received radiation therapy underwent moderate-to-severe skin reactions such as non-healing wounds, severely reducing patients' quality of life and adversely affecting their disease treatment. Wound healing is significantly delayed in irradiated skin. Fibronectin was the most significantly and consistently downregulated in radiation-damaged skin. From a murine model, we confirmed that radiation leads to decreased fibronectin expression in the skin as well as delayed wound healing. Topically fibronectin was found to significantly improve wound healing in irradiated skin and was associated with decreased inflammatory infiltrate and increased angiogenesis. Fibronectin treatment may be a useful adjunctive modality in the treatment of non-healing radiation wounds. Besides, this review study can be referenced for clinicians to treat RSIs to guide subsequent clinical application.

Keywords Topical Fibronectin, Radiation skin injury, Platelet-rich plasma, MMP & TNF-α.

I. INTRODUCTION

In the present review study, the role of topical fibronectin in radiation-induced skin reactions (RISR) or radiation ulcer (RU) was discussed. Radiation ulcer is a common adverse effect of a large dose of radiation for bone marrow transplant or cancer radiotherapy[1-3]. These chronic wounds can last for several years and cause great distress to patients[4-6]. Currently, patients have a potent topical application "*Fibronectin Skin Antibacterial Liquid*" which is marketed in India as Fibrega for the first time by PRG pharma private Limited.

Radiation therapy can be adopted to target effectively tumors. Radiation not only has a damaging effect on tumor cells but it inevitably affects the normal tissue cells in the irradiation field. During radiotherapy treatment, to a certain extent, a wide range of radiation doses, various radiation, energy of the radiation, treatment time of the radiation, and course of treatment overall affected the patient. Patients

having undergone radiotherapy may develop different skin damage as impacted by their different ages, physical conditions, skin types, as well as location and duration of exposure. Despite the increasing accuracy of radiation therapy, normal tissues are still unavoidably exposed. The main causes of RSI include nuclear radiation accidents, radiotherapy, and occupational exposure.

MECHANISM OF RADIOTHERAPY CYCLE DURING SKIN HEALING IN IRRADIATED SKIN

Early skin reactions after radiotherapy are usually moderate, but over 90% of patients treated with radiotherapy develop skin reactions[7]. These reactions appear in the early stages as erythema and as dry desquamation. If no infection occurs, re-epithelialization will begin within 10 days. Within two months, edema and inflammatory exudates will subside, and an area of brown pigmentation will be seen[8]. Moist desquamation is characterized by a painful peeling skin with exposure of the dermis, exudate production and ulceration.

Moist desquamation is observed in <10% of patients and is dose-dependent[9]. Ideally, surviving germinal cells regenerate to repopulate the epidermis and allow for healing. However, when this repopulation fails, an acute ulcer in radiated skin will occur. Since the introduction of megavoltage linear accelerators, skin reactions rarely deteriorate to the ulceration stage, because the maximum deposited dose to the skin is at 0.5-4 cm below. One year after radiation, the epidermis will appear dry, thin, and semi translucent. Hair follicles and sebaceous glands are usually absent. Fibrosis of the skin is present. The lymphatics are absent or blocked by fibrous tissue.

Myocytes develop vacuoles and the muscles become scarred containing very few vessels. Years after radiation therapy, delayed ulcers and malignancies may occur. Delayed ulcers are more common than acute ulcers and may exist for several years. Commonly, the late skin reaction is characterized as fibrosis, atrophy, contraction, induration and a dose-dependent decrease in wound tensile strength. Poor wound healing can even lead to death, which may be from carotid artery rupture or to prolonged morbidity from fistula formation, wound dehiscence, skin flap reconstructive failure, and skin necrosis.

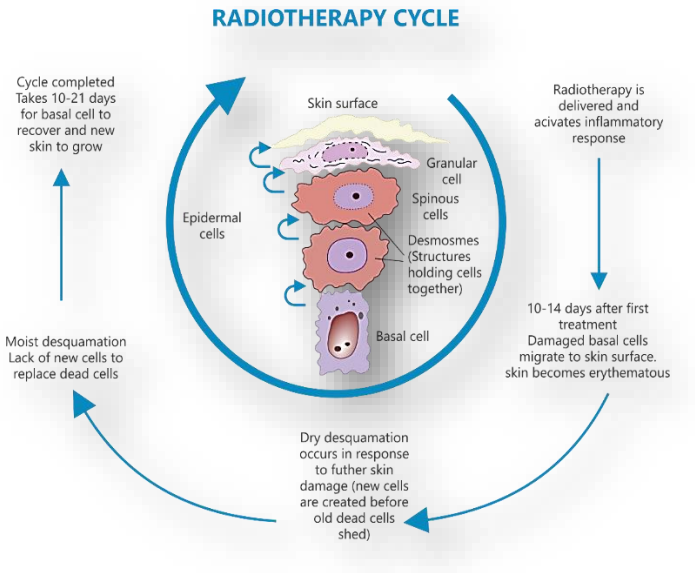


Figure 1 : Show Mechanism of radiotherapy cycle through 4 Grade

Grade 1	Grade 2	Grade 3	Grade 4
Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

Any localized trauma, surgery or infection to the irradiated skin can lead to a major non-healing wound. There is a great variability in the risk of developing radiation side effects. In part, this can be ascribed to differences in treatment and in patient characteristics[7]. However, the pathophysiology of wound healing in the radiated skin is for the most part only theoretical. It is beyond controversy that histopathological changes like impaired neovascularization and excessive fibrosis are essential causes, particularly

with regard to the late side effects of radiotherapy. By the same token, it is clear that many of the observed changes, in the side effects are elicited by the activation or deactivation of growth factors and cytokines.

Ionizing radiation changes their interactions and cascades. IL-1, which is primarily secreted by macrophages and keratinocytes, is also directly activated by ionizing radiation. IL-1 stimulates keratinocytes and fibroblasts as well as MMPs. It has been demonstrated that ionizing radiation is able to induce the release of TNF-α by different cell types. TNF-α is a potent activator of neutrophils, stimulates the proliferation of fibroblasts and induces the synthesis of MMPs. Decreased proliferation, impaired angiogenesis, and persistently high concentrations of MMPs were recently seen in an in vitro analysis of radiation-induced dermal wounds [10-12]. The impact that growth factors and cytokines have in radiation-induced wound healing disorders is obvious. Further studies are necessary, but in the last few years it has become clear that there is an important and direct genetic component[13-15].

These correlations shall be outlined using fibrosis as the example. Changes in collagen metabolism apparently have an important role in fibrosis formation. Elevated TGF-β1 levels are correlated with an increased risk of fibrosis. As collagen is the major structural protein and composes 70-80% of the dry weight of the skin, modulation of skin collagen metabolism by therapeutic irradiation has clinical importance. Skin collagen, synthesized by fibroblasts, is comprised from 80-85% type I and of 10-15% type III collagen[16-18]. Single nucleotide polymorphisms (SNPs) account for most of the known genetic variations between individuals and are usually defined as polymorphisms in which the minor variant (allele) is present in at least 1% of a given population. SNPs can affect protein function by altering the amino acid composition or by affecting various aspects of transcriptional and translational control[19].

Table 1 Possible key factors affected by radiotherapy with respect to the phases of wound

Phase of wound healing	Factors affected by radiation therapy
Inflammation	TGFβ, VEGF, interleukin-1, interleukin-8, TNFα, IFN-γ
Proliferation	TGFβ, VEGF, EGF, FGF, PDGF, NO
Remodelling	MMP-1, MMP-2, MMP-12, MMP-13, TIMP

Wound healing factors affected by radiation therapy.

ROLE OF FIBRONECTIN IN RADIOTHERAPY

Unlike ordinary burns and ulcers, radiation directly damages the skin as well as its deep tissue cells, causing dryness, loss of elasticity, pigmentation, soft tissue fibrosis, capillary dilatation, and radiation dermatitis in irradiated areas. Moreover, it irreversibly damages microvascular and small blood vessel endothelial cells in skin tissue. As a result, patients' damaged skin does not heal for a long time, and it exhibits susceptibility to infection. The lesion eventually develops into fibrosis of the skin tissue and even becomes cancerous, significantly deteriorating patients' quality of life. Numerous existing medication and dressings are available to prevent and treat radioactive skin damage (e.g., corticosteroids, hyaluronic acid, triethanolamine, sucralfate cream, aloe, calendula cream, as well as water-based cream). But failed to heal the radiation ulcer. Fibronectin downregulation – the penultimate reason for development of skin damage in irradiated skin[20].

To assess whether there is a pattern of protein dysregulation in radiation-damaged skin. To further investigate the relationship between radiation and fibronectin expression in skin, we utilized a murine model of chronic radiation skin injury.

Fibronectin, the only protein responsible for mediating the skin healing process across all steps, is the most significantly and consistently downregulated molecule in radiation-damaged skin. Fibronectin presence is essential for skin repair in an orderly sequence of three phases: inflammation, proliferation, and remodeling; radiation impairs this sequence, inhibiting the normal damage healing process by direct damage and subsequent depletion in Fibronectin levels at the site of exposure leading to abnormal collagen deposition with loss of adnexal structures, disordered vasculature, and dysfunctional chronic inflammation. The constitution and function of dermal extracellular matrix (ECM) is critical to wound healing.

However, radiation impairs this sequence, inhibiting the normal wound healing process. During the inflammatory phase, tissue levels of various cytokines and chemokines involved in normal wound healing, including VEGF, TGF-β, TNF-α and IFN-γ, are deranged[21]. Additionally, the generation of reactive oxygen species leads to endothelial damage and dysfunction, producing progressive vasculopathy and impairing the formation of granulation tissue, re-epithelialization, and neovascularization that characterizes the proliferative phase[21]. Moreover, fibroblasts, which comprise a crucial role in the remodeling phase of collagen deposition and remodeling, produce highly disorganized collagen framework leading to impaired wound strength[22-23]. The culmination of these negative effects of radiation on wound healing manifests clinically as atrophic, dry pigmented skin that is commonly fibrotic or ulcerated, healing poorly or not at all[24]. The mechanism of radiation-induced skin fibrosis is complex, and involves terminal differentiation of fibroblasts, abnormal collagen deposition with loss of adnexal structures, disordered vasculature, and dysfunctional chronic inflammation. The constitution and function of the dermal extracellular matrix (ECM) is critical to wound healing[16]. Irradiation results in permanent and intrinsic damage to fibroblasts, the primary cell type responsible for the production of ECM[25-26]. These changes are associated with characteristic alterations in ECM protein composition and breaking strength, both acutely and over time[23,28]. In the present study (in murine wound model), we found that fibronectin was among the most significantly downregulated proteins in irradiated skin. Fibronectin is an ECM glycoprotein that is involved in a number of cellular mechanisms important to wound healing, including cell growth and migration, and serves as a binding site for a number of growth factors[29-31]. It promotes wound healing and is protective against irradiation[32-36]. Furthermore, topical application of fibronectin led to significantly improved healing in irradiated wounds. This was associated with a significant reduction in acute inflammation and an increase in angiogenesis. These findings suggest that fibronectin may be involved in the pathogenesis of poor wound healing after radiation skin injury, and that exogenous supplementation may assist in the repair of radiation-damaged tissue.

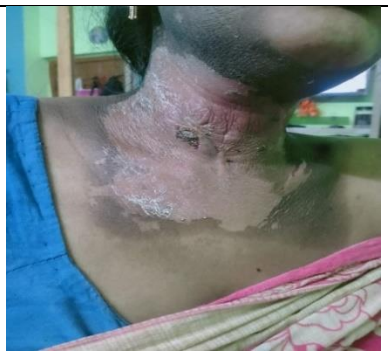
CURRENT CASE STUDY OF TOPICAL APPLICATION IN THE TREATMENT OF RADIATION SKIN INJURY

In murine wound model study, there was some evidence to suggest that fibronectin levels are altered after exposure to ionizing radiation in non-skin tissues37-39. We demonstrated that fibronectin was downregulated in response to radiation in mouse skin. Patients who undergo radiotherapy are not able to heal radiation ulcers by their own or some existing medication and dressings are available to prevent and treat radioactive skin damage. Exogenous fibronectin contains active fibronectin which is derived from Plasma by apheresis.

Topical application of fibronectin to wounds with similarly diminished levels of the protein resulted in significantly improved wound healing. These findings

elucidate a potential target for therapy in the prevention or treatment of radiation skin injury and irradiated wounds. Given the clinical challenges associated with non-healing radiation wounds, further efforts towards understanding the mechanism of improved wound healing after application of fibronectin will be important in facilitating clinical development of fibronectin-based treatments[37-39].

Case Study 1:

Type of Wound	Radiation induced Skin Reaction	
Patient	45year-old Female	
Application use (Fibrega)	**Before**	**After**
		
	Day 0 (Image #1)	Day 7 (Image #2)
Introduction	A 45-year old Female, suffered with throat Cancer after 1 week of Radiotherapy patient developed skin reaction (Image #1); The total planned radiotherapy is for 45 days; the therapy is ongoing everyday.	
Result	Patient assessment and history indicated a whole necrosis tissue present around the treated area after radiotherapy. • Death of tissue. • Highly brittle and malodorous. After radiotherapy check the irradiation site for cleanliness and dryness, if required perform gentle cleaning and pat dry. Use an FN application over the affected surface. After 7 days (Image #2), fresh skin was formed at the area where FN application was applied, the Radiotherapy is ongoing. No secondary dressing is required, however if needed, use a paraffin based dressing as directed by the doctor.	
Conclusion	Significant improvements in the cure rates, shortened hospital stay, but also a reduction in patient's pain and financial burden. It is now understood that radiotherapy affects the surrounding healthy tissue and delayed wound healing.	

Case Study 2:

Type of Wound	Radiation induced Skin Reaction	
Patient	53year-old male	
Application use (Fibrega)	**Before**	**After**
		
	Day 0 (Image #3)	Day 7 (Image #4)
Introduction	A 53-year old male with a history of Ca Glottis for long years presents and ulceration. Grade 3 Dermatitis (Image #3) treated with FN application. The skin discoloration associated with radiation injury. Irradiated skin heals significantly slower than normal skin at Radiation Ulcer. Topical application of fibronectin at the time of wounding is associated with significantly accelerated wound healing.	
Result	Patient assessment and history indicated a whole necrosis tissue present around the treated area after radiotherapy. • Death of tissue. • Highly brittle and malodorous. After radiotherapy check the irradiation site for cleanliness and dryness, if required perform gentle cleaning and pat dry. Grade 3 Dermatitis treated with FN application. The wound continued to progress and was completely epithelialized at 7 days (Image #4) & showed no recurrence with normal skin lines returning (Images #4). No secondary dressing is required, however if needed, use a paraffin based dressing as directed by the doctor.	
Conclusion	The clinical observation results show that the FN topical spray has a significant effect on the treatment of refractory ulcers, which can accelerate healing, shorten the course of treatment, and find no side effects. FN solution can effectively inhibit bacterial infection. Other products take longer time to heal the wound compared to the topical application which was found to be easy and quick to use to the entire wound care team helping to simplify the delivery of wound preparation.	

II. FUTURE ASPECTS

Research into new therapeutic approaches to treat radiation skin injury ulcers includes: topical administration of Fibronectin in the treatment of irradiated wounds. Topical application of fibronectin is golden therapy for the patients with non-healing radiation ulcers. The clinical challenge to optimize wound healing in irradiated patients remains. The present paper critically reviews and summarizes the literature concerning the biology and possibly therapeutic strategies of radiation-induced compromise in wound healing, including topical application of fibronectin.

III. DISCUSSION

Complications of radiotherapy pose a significant problem for patients and physicians. Since the mechanism of pathogenesis for radiation skin injury has not been fully elucidated, few targeted therapies exist for this problem in clinical practice. But fail to heal the radiation ulcer is widely caused by ionizing radiation therapy. This suggests that microvascular damage and tissue hypoxia may be transient, fuelling research on the impact of radiation on other skin-specific factors. The dermal extracellular matrix and its constituent cells and proteins are critical to skin homeostasis, skin pathology, and wound healing. ECM functions are mediated by a wide variety of mechanisms, including providing a suitable microenvironment for resident cells and binding and/or releasing important growth factors25. As a result, irradiation's effect on fibroblasts and associated ECM production are frequent areas of research. Ionizing radiation has been shown to result in diminished growth and function of fibroblasts independent of blood supply26-27.

In this report, Fibronectin was the most consistently and significantly downregulated. Like collagen, fibronectin is an ECM glycoprotein predominantly produced by dermal fibroblasts29. Also, like collagen, fibronectin contains a number of binding sites for growth factors, including FGF, VEGF, and PDGF, which have been shown to promote wound healing and protect against radiation tissue injury43-46. As a result, there have been a number of studies demonstrating fibronectin's role in the promotion of wound healing30,33-36. Though the underlying mechanism has not been fully elucidated, evidence suggests that fibronectin can form a scaffold for epidermal cell migration and modulate cytokines and growth factors in the tissue30,34,36. Exposure to ionizing radiation has been associated with altered fibronectin levels in other end-organs37-39. As a result, additional research is required to evaluate how downregulation of fibronectin in irradiated skin affects downstream mediators of cell proliferation and migration. We applied topical fibronectin to irradiated wounds, topical fibronectin healed significantly faster in radiation ulcer. Histological analysis demonstrated that this was associated with a decrease in acute inflammatory infiltrate and increase in angiogenesis, resulting in an improved healing score in radiation ulcer.

These findings are consistent with fibronectin's known involvement in the storage and release of growth factors and cytokines, which may account for the immunomodulatory and angiogenic effect of topical fibronectin in these wounds. Both TGF-β and SMAD3 have been repeatedly implicated as fundamental mediators of radiation-induced fibrosis. Further, intervention in the TGF-β/SMAD3 pathway results in improved wound healing in irradiated skin40-41. Both molecules were significantly upregulated in irradiated skin, and may serve as a potential target for topical fibronectin's effects. In a murine irradiated wound model, topical application of fibronectin to wounds with similarly diminished levels of the protein resulted in significantly improved wound healing. These findings elucidate a potential target for therapy in the prevention or treatment of radiation skin injury and irradiated wounds. Given the clinical challenges associated with non-healing

radiation wounds, further efforts towards understanding the mechanism of improved wound healing after application of fibronectin will be important in facilitating clinical development of fibronectin-based treatments.

IV. CONCLUSION

In brief, RISR is a more common radiation therapy complication. Wound healing in irradiated tissues is a common and challenging clinical problem. Generally accepted guidelines for necrotic tissue management, infection prevention and treatment, wound exudate management, and reassessment of treatment plans based on observation of wound progress should be conducted to treat full thickness wounds resulting from delayed radiation injury. Topical Fibronectin has thus shown to effectively address this concern of delayed skin healing by replenishing the site with Bioavailable Plasma Fibronectin. Patient education should consist of daily skin and wound care management and topical medications. More cost-effective protective measures exerting fewer side effects should be developed to effectively protect the interests of patients, ensure smooth chemotherapy, as well as improving the quality of life of patient.

V. REFERENCES

[1]. Han, G. et al. Preventive and therapeutic effects of Smad7 on radiation-induced oral mucositis. Nat. Med. 19, 421–428 (2013).

[2]. Sonis, S. T. Efficacy of palifermin (keratinocyte growth factor-1) in the amelioration of oral mucositis. Core Evid. 4, 199–205 (2010).

[3]. Vagliano, L. et al. Incidence and severity of oral mucositis in patients undergoing haematopoietic SCT—results of a multicentre study. Bone marrow Transplant. 46, 727–732 (2011).

[4]. Feldmeier, J. J. et al. Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities. Undersea Hyperb. Med.: J. Undersea Hyperb. Med. Soc., Inc. 27, 15–19 (2000).

[5]. Li, Z. & Maitz, P. Cell therapy for severe burn wound healing. Burns trauma 6, 13 (2018)

[6]. Yang, H. et al. Investigation and analysis of the characteristics and drug sensitivity of bacteria in skin ulcer infections. Chin. J. Traumatol.Zhonghua chuang shang za zhi 20, 194–197 (2017).

[7]. Olascoaga A, Vilar-Compte D, Poitevin-Chacon A and Contreras- Ruiz J: Wound healing in radiated skin: pathophysiology and treatment options. Int Wound J 5: 246-257, 2008.

[8]. McLean AS: Early adverse effects of radiation. Br Med Bull 29: 69-73, 1973.

[9]. Behrends U, Peter RU, Hintermeier-Knabe R, et al: Ionizing radiation induces human intercellular adhesion molecule-1 in vitro. J Invest Dermatol 103: 726-730, 1994.

[10]. Hallahan DE, Spriggs DR, Beckett MA, Kufe DW and Weichselbaum RR: Increased tumor necrosis factor alpha mRNA after cellular exposure to ionizing radiation. Proc Natl Acad Sci USA 86: 10104-10107, 1989.

[11]. Sherman ML, Datta R, Hallahan DE, Weichselbaum RR and Kufe DW: Regulation of tumor necrosis factor gene expression by ionizing radiation in human myeloid leukemia cells and peripheral blood monocytes. J Clin Invest 87: 1794-1797, 1991.

[12]. Goessler UR, Bugert P, Kassner S, et al: In vitro analysis of radiation-induced dermal wounds. Otolaryngol Head Neck Surg 142: 845-850, 2010.

[13]. West CM, Elliott RM and Burnet NG: The genomics revolution and radiotherapy. Clin Oncol (R Coll Radiol) 19: 470-480, 2007.

[14]. Fernet M and Hall J: Genetic biomarkers of therapeutic radiation sensitivity. DNA Repair (Amst) 3: 1237-1243, 2004.

[15]. Riekki R, Jukkola A, Sassi ML, Hoyhtya M, Kallioinen M, Risteli J and Oikarinen A: Modulation of skin collagen metabolism by irradiation: collagen synthesis is increased in irradiated human skin. Br J Dermatol 142: 874-880, 2000.

[16]. Riekki R, Harvima IT, Jukkola A, Risteli J and Oikarinen A: The production of collagen and the activity of mast-cell chymase increase in human skin after irradiation therapy. Exp Dermatol 13: 364-371, 2004.

[17]. Autio P, Saarto T, Tenhunen M, Elomaa I, Risteli J and Lahtinen T: Demonstration of increased collagen synthesis in irradiated human skin in vivo. Br J Cancer 77: 2331-2335, 1998.

[18]. Popanda O, Marquardt JU, Chang-Claude J and Schmezer P: Genetic variation in normal tissue toxicity induced by ionizing radiation. Mutat Res 667: 58-69, 2009.

[19]. Kishore U, Bernal AL, Kamran MF, Saxena S, Singh M, Sarma PU, Madan T and Chakraborty T: Surfactant proteins SP-A and SP-D in human health and disease. Arch Immunol Ther Exp (Warza) 53: 399-417

[20]. Zhang Y, Zhang S, Shao X. Topical agent therapy for prevention and treatment of radiodermatitis: a meta- analysis. Support Care Cancer. 2013; 21:1025–31. https://doi.org/10.1007/s00520-012-1622-5 PMID:23064885

[21]. Barker, H. E., Paget, J. T., Khan, A. A. & Harrington, K. J. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer. 15, 409–425, doi:10.1038/nrc3958 (2015).

[22]. Herskind, C., Bamberg, M. & Rodemann, H. P. The role of cytokines in the development of normal-tissue reactions after radiotherapy. Strahlenther Onkol. 174(Suppl 3), 12–15 (1998).

[23]. Illsley, M. C., Peacock, J. H., McAnulty, R. J. & Yarnold, J. R. Increased collagen production in fibroblasts cultured from irradiated skin and effect of TGF beta (1)- clinical study. Br J Cancer. 83, 650–654, doi:10.1054/bjoc.2000.1321 (2000).

[24]. Haubner, F., Ohmann, E., Pohl, F., Strutz, J. & Gassner, H. G. Wound healing after radiation therapy: review of the literature. Radiat Oncol. 7, 162, doi:10.1186/1748-717X-7-162 (2012).

[25]. Schultz, G. S. & Wysocki, A. Interactions between extracellular matrix and growth factors in wound healing. Wound Repair Regen. 17, 153–162, doi:10.1111/j.1524-475X.2009.00466.x (2009).

[26]. Rudolph, R., Arganese, T. & Woodward, M. The ultrastructure and etiology of chronic radiotherapy damage in human skin. Ann Plast Surg. 9, 282–292 (1982).

[27]. Rudolph, R., Vande Berg, J., Schneider, J. A., Fisher, J. C. & Poolman, W. L. Slowed growth of cultured fibroblasts from human radiation wounds. Plast Reconstr Surg. 82, 669–677 (1988).

[28]. Bernstein, E. F. et al. Healing impairment of open wounds by skin irradiation. J Dermatol Surg Oncol. 20, 757–760 (1994).

[29]. Pankov, R. & Yamada, K. M. Fibronectin at a glance. J Cell Sci 115, 3861–3863, doi:10.1242/jcs.00059 (2002).

[30]. Clark, R. A. et al. Fibronectin and fibrin provide a provisional matrix for epidermal cell migration during wound reepithelialization. J Invest Dermatol. 79, 264–269 (1982).

[31]. Zhu, J. & Clark, R. A. Fibronectin at select sites binds multiple growth factors and enhances their activity: expansion of the collaborative ECM-GF paradigm. J Invest Dermatol 134, 895–901, doi:10.1038/jid.2013.484 (2014).

[32]. Cordes, N. & Beinke, C. Fibronectin alters cell survival and intracellular signaling of confluent

A549 cultures after irradiation. Cancer Biol Ther. 3, 47–53 (2004).

[33]. Cordes, N., Blaese, M. A., Plasswilm, L., Rodemann, H. P. & Van Beuningen, D. Fibronectin and laminin increase resistance to ionizing radiation and the cytotoxic drug Ukrain in human tumour and normal cells in vitro. Int J Radiat Biol. 79, 709–720 (2003).

[34]. Martino, M. M. et al. Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. Sci Transl Med. 3, 100ra189, doi:10.1126/scitranslmed.3002614 (2011).

[35]. Moroz, A. & Deffune, E. Platelet-rich plasma and chronic wounds: remaining fibronectin may influence matrix remodeling and regeneration success. Cytotherapy. 15, 1436–1439, doi:10.1016/j.jcyt.2013.05.019 (2013).

[36]. Tortelli, F., Pisano, M., Briquez, P. S., Martino, M. M. & Hubbell, J. A. Fibronectin binding modulates CXCL11 activity and facilitates wound healing. PLoS One. 8, e79610, doi:10.1371/journal.pone.0079610 (2013).

[37]. Finkelstein, J. N., Johnston, C. J., Baggs, R. & Rubin, P. Early alterations in extracellular matrix and transforming growth factor beta gene expression in mouse lung indicative of late radiation fibrosis. Int J Radiat Oncol Biol Phys. 28, 621–631 (1994).

[38]. Meznarich, H. K., McCoy, L. S., Bale, T. L., Stiegler, G. L. & Sikov, M. R. Brain fibronectin expression in prenatally irradiated mice. J Toxicol Environ Health. 40, 263–275, doi:10.1080/15287399309531793 (1993).

[39]. Nishioka, A., Ogawa, Y., Inomata, T., Maeda, T. & Seguchi, H. Fibronectin expression in cancer tissues from patients undergoing radiation therapy. Histol Histopathol. 8, 457–462 (1993).

[40]. Spurrier, B., Ramalingam, S. & Nishizuka, S. Reverse-phase protein lysate microarrays for cell signaling analysis. Nat Protoc. 3, 1796–1808, doi:10.1038/nprot.2008.179 (2008).

[41]. Flanders, K. C. et al. Interference with transforming growth factor-beta/Smad3 signaling results in accelerated healing of wounds in previously irradiated skin. Am J Pathol. 163, 2247–2257 (2003).

[42]. Martin, M., Lefaix, J. & Delanian, S. TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys. 47, 277–290 (2000).

[43]. Greenhalgh, D. G., Sprugel, K. H., Murray, M. J. & Ross, R. PDGF and FGF stimulate wound healing in the genetically diabetic mouse. Am J Pathol. 136, 1235–1246 (1990).

[44]. Kinoshita, N. et al. The usefulness of basic fibroblast growth factor for radiation-exposed tissue. Wound Repair Regen. 20, 91–102, doi:10.1111/j.1524-475X.2011.00758.x (2012).

[45]. Mustoe, T. A. et al. Reversal of impaired wound healing in irradiated rats by platelet-derived growth factor-BB. Am J Surg. 158, 345–350 (1989).

[46]. Nissen, N. N. et al. Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. Am J Pathol. 152, 1445–1452 (1998).

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