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A critical study on ionizing radiation sensitive protein biomarkers and mechanisms of radiation-induced normal tissue toxicity implications for clinical trials

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Abstract
Outline: The present understanding of the mechanisms of radiation-induced harm in the normal tissue and the available medical treatments to lessen its severity. Higher radiation doses can now be delivered to well-defined tumor target tissues because to advancements in radiation delivery using megavoltage and intensity-modulated radiation treatment. However, the curative treatment of malignancies has a significant danger of damaging vital normal tissues and organs, particularly when radiation and chemotherapy are combined. Depletion of stem tissue and progenitor cells as well as injury to vascular endothelial micro vessels are the main causes of pathogenesis. The recovery and repopulation of stromal stem cells may be chronically hampered by long-lived free radicals, reactive oxygen/nitrogen species, and pro-inflammatory cytokines/chemokines, leading to progressive damage after radiation exposure, according to emerging theories of radiation-induced normal tissue toxicity. It may be possible to gain new insight into the pathogenesis of radiation-induced tissue damage by better understanding the mechanisms governing interactions between excessive reactive oxygen species production, pro-inflammatory cytokine production, activated macrophages, and the role of bone marrow-derived progenitor and stem cells. New targets for preventing or reducing radiation injury to tissues and organs might become apparent with a deeper understanding of the molecular signaling pathways of cytokines and chemokines.

Keywords: Ionizing radiation, normal tissue, biomarker, radiotherapy, radio sensitivity, proteomics

Introduction
Ionizing radiation is being used more frequently in therapeutic and diagnostic treatments in medicine. According to the IARC Global Cancer Observatory (https://gco.iarc.fr/), there were more than 18 million new cases of cancer in 2018 [1]. and 50–60% of malignancies are treated with radiation (RT) [2]. The total exposure to medical imaging and image-guided therapies has increased six-fold in the USA since 1980 [3]. However, little is known about the possible negative health effects of radiation exposure for both patients and medical personnel, particularly with regard to individual variances in radio sensitivity.

The response of cells, tissues, or persons to ionising radiation is measured as radio sensitivity (IR). When compared to most other "normal" responding subjects, subjects with higher reactions are referred to as radiosensitive [4, 5, 6]. Inflammation, fibrosis, cardiovascular disease, cataracts, and cognitive imparment are some of the reactions [7].

The frequency and severity vary from person to person and can be influenced by both genetic and lifestyle factors. The use of RT is restricted in 5–10% of patients due to the occurrence of acute, clinically varied, significant radiogenic side effects on normal tissue in the radiation field, which might result in subpar tumour control or gravely damage patient quality of life [8, 9, 10]. Treatment would be improved if radiosensitive patients could be accurately identified prior to treatment so that a customized dose adjustment could be used. Additionally, identifying those who are radiosensitive would be a crucial step in protecting those who are exposed to radiation at work. Individual differences in radiation sensitivity have been identified as a major area for future research by two radiation research platforms: the Multidisciplinary European Low Dose Initiative (MELODI) and the European Alliance Medical Radiation Protection Research (EURAMED).

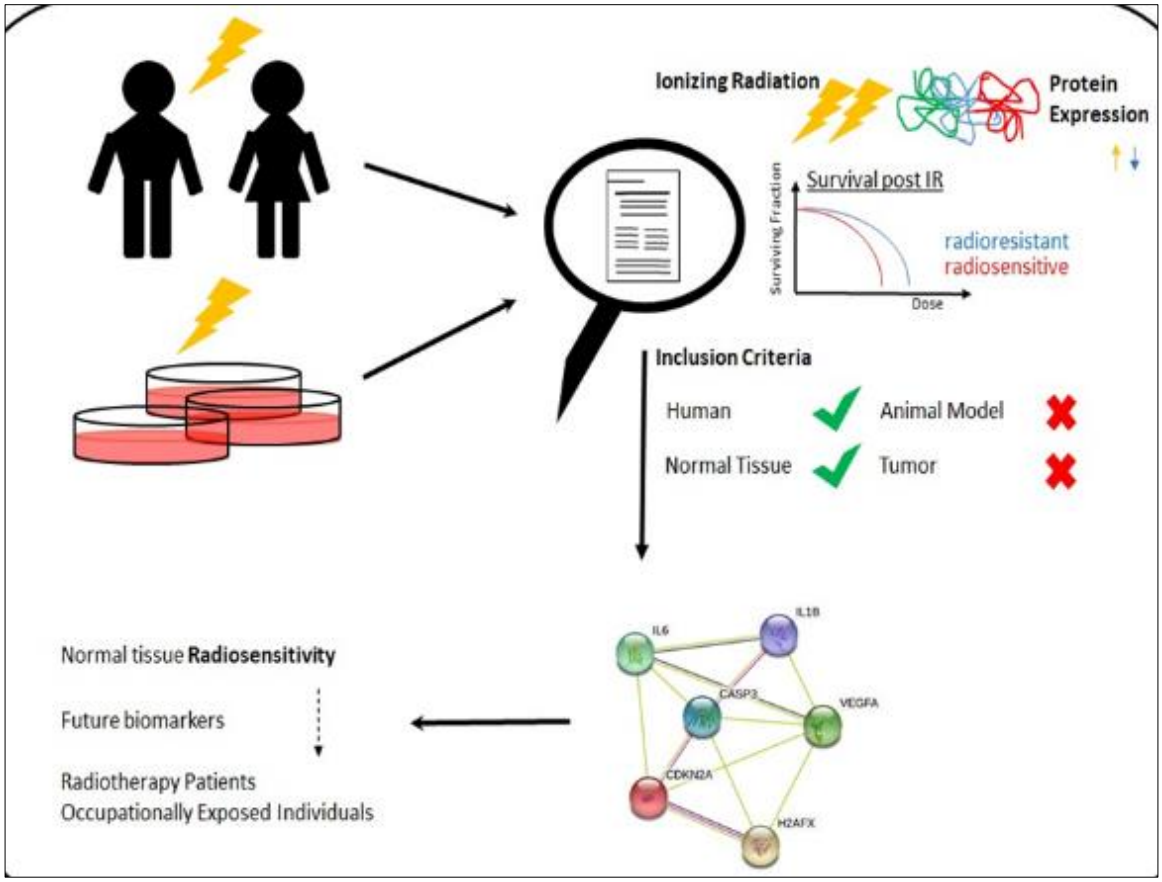

Fig 1: Ionizing radiation sensitivity

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Radiation-induced tissue damage pathogenesis

There have been endeavors to distinguish whether parenchymal or endothelial begetter's cells are the essential targets liable for the tissue harm. Generally, typical tissue injury following high portions of radiation is remembered to result from one or the other consumption of parenchymal and additionally vascular endothelial cells. The previously mentioned issue has been tended to using boron neutron catch treatment in one clever radiobiological study [1]. The method depends on the short-run alpha particles created by the steady boron isotope's neutron catch process. Since the blood cerebrum hindrance (BBB) forestalls the boronated substance from arriving at the mind parenchyma, particular light of the microvasculature was achieved by intraperitoneal conveyance of a boron compound that stays inside the endothelium. With just a little measurement to parenchymal glial cells, the particular vascular harm from the boron neutron catch light caused impressive demyelination and white matter rot, demonstrating that endothelial cell misfortune assumes a critical part in this pathogenesis. In any case, it is charming to take note of that endothelial cell obliteration isn't the reason for the possible improvement of the gastrointestinal disease [3] or that designated light of vascular endothelium has no impact on the endurance of mouse digestive sepulcher immature microorganisms.

Later sub-atomic and cell examinations battle that unique optional responsive components in response to the demise of tissue stem and ancestor cells and vascular endothelial cells bring about essentially expanded cell misfortune, tissue harm, fibrosis, rot, and practical weaknesses. The powerful communications between radiation-actuated target cell demise, the creation of receptive oxygen species (ROS), and resulting auxiliary receptive supportive of fiery cycles and natural resistant reactions are portrayed in Fig. 1. These cycles are believed to be engaged with particular cell misfortune, tissue harm, and utilitarian shortages.

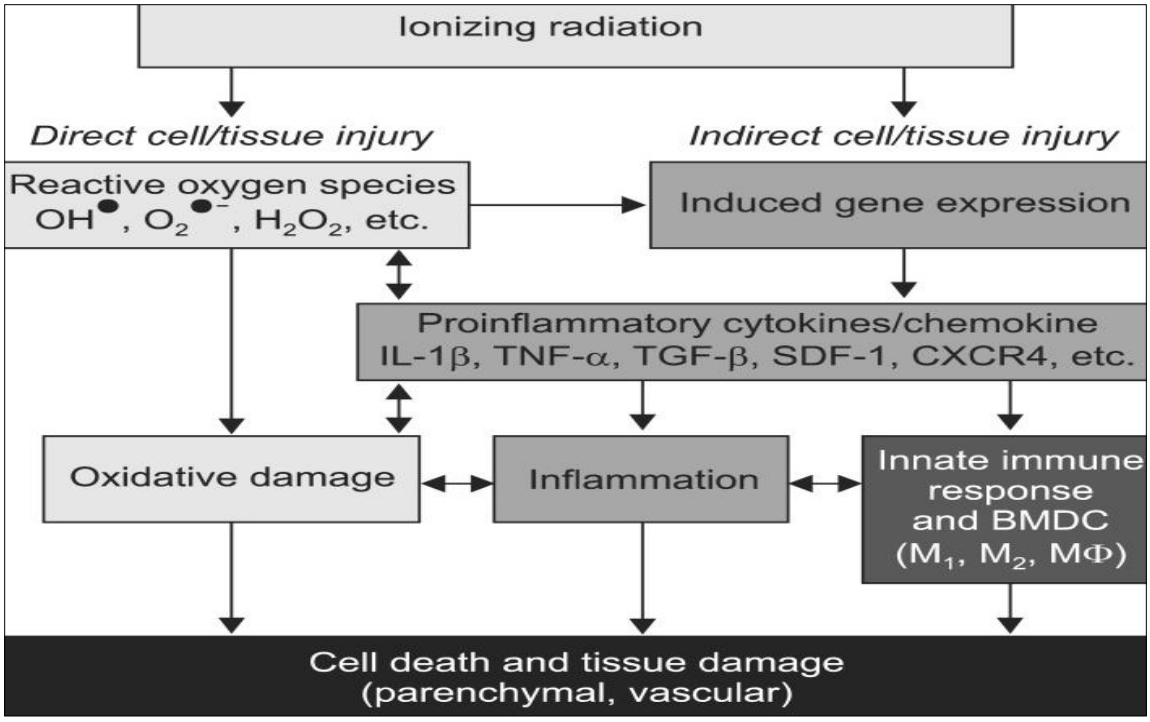

Fig 2: illustrates the dynamic interactions involving radiation-induced death of target cells

Bone marrow-derived cells' function in damage to normal tissue

The deficiency of parenchymal cells and vascular endothelial harm, which might lessen tissue perfusion, is the notable histological changes connected to radiation-actuated tissue harm, as was featured in the conversation of pathogenesis in typical tissues and organs that was recently referenced (hypoxia). Specifically, the underlying vascular injury, which shows bit by bit over numerous months, is one of the principal supporters of the late impacts of radiation injury. Angiogenesis and vasculogenesis are the two frameworks that can fix vascular injury [15]. Endothelial cells that are now present multiply and move because of cytokines and development factors cooperating to drive angiogenesis. Vasculogenesis is the most common way of making veins without any preparation and is described by the enlistment of cells with endothelial ancestor cell potential. Bone marrow determined cells BMDC are specially selected to the injured area because of neighborhood tissue injury, including radiation, as indicated by mounting proof [16, 17]. As a rule, the over expression of SDF-1 and CXCR4 harmonizes with the planning of the enlistment and homing of the prepared BMDC into the illuminated tissue [16]. Following nearby light, three unmistakable sub-populaces of BMDC - mesenchymal undifferentiated organisms, endothelial begetter cells, and myelomonocytic cells - are selected. Late examination has shown that most of BMDC that migrate to illuminated tissues, like skin, lung, mind, and bone marrow, are myelomonocytic cells that display the group of separation (Cd) surface marker CD11b. Myelomonocytic cells have attributes of the macrophage heredity relying upon the nearby tissue microenvironment [20]. Albeit these CD11b-communicating cells don't coordinate into the veins, they in all actuality do deliver angiogenic factors that explicitly drive paracrine-intervened vessel creation and fix. Then again, some CD11b-communicating cells can weaken tissue recovery by setting off a torrential slide of incendiary cytokines.

Macrophages are urgent to the invulnerable framework's capacity to answer tissue harm, assisting with controlling aggravation, resolve issues, and fix harmed tissue. Macrophages settle close to the site of radiation-prompted tissue harm and might be associated with a torrential slide of provocative cytokines. There are two kinds of macrophage aggregates: "traditionally initiated favorable to fiery (M1)" and "on the other hand enacted" calming (M2)" cells. While M2 macrophages support extracellular network combination, cell expansion, and angiogenesis, M1 macrophages support aggravation, extracellular framework breakdown, and apoptosis. While M2 macrophages tend to diminish aggravation and advance injury recuperating, M1 macrophages frequently cause tissue harm and tenacious irritation (fibrosis). As indicated by Jaal *et al*., skin tissue presented to radiation showed upgraded CD105-communicating macrophage action for quite some time following openness. Furthermore, we have information showing raised macrophage action in the illuminated skin, starting 3 days after a solitary portion of 30 Gy in mice and going on for over 2 months a while later (upheld by the recognition of raised levels of the 160 kD glycoprotein, F4/80, communicated by enacted macrophage). Both the intense and sub-intense periods of skin harm saw an over expression of MMP9. Radiation skin injury and radiation lung injury were decreased by utilizing liposomal clodronate to forestall macrophage invasion [19].

Radiation's skin injury: clinical and pathological manifestations

Early erythema and dry or wet desquamation are signs of acute radiation damage to the skin, which is also caused by the depopulation of the basal epithelial cells that are acutely reacting. Such severe skin reactions typically go away with time. Some moist lesions do, however, later develop into sub-acute and late stages of skin damage. Skin injuries may only affect a small region, but they can penetrate deep into the soft tissue and even reach the underlying muscle and bone. Based on the radiation dose, the symptoms that follow

might range from dry desquamation or ulceration to necrosis when the basal layer is repopulated by the proliferation of surviving clonogenic cells. At doses more than a single dosage of 20–25 Gy or fractionated doses of 70 Gy or higher, late effects-typically occurring months to years after exposure-occur. Teleangiectasia, extensive dermal fibrosis, sebaceous and sweat gland atrophy, hair follicle loss, and, with higher doses, increased melanin deposition or depigmentation and skin ulcers, are the main underlying histological findings at the chronic stage.

The pathologic effects seen in the irradiated skin are believed to be caused by the loss of stem and progenitor cells of the basal and dermal layers and multicellular interactions through a variety of inflammatory mediators that result in fibrotic processes. This is despite the fact that the precise cellular mechanisms underlying radiation-induced skin injury are still poorly understood. The diminished ability of tissue stem cells to replenish differentiated functional cells, which results in the loss of homeostasis, is one cause of radiation damage to the skin. A 3-fold increase in apoptosis among these cells remains for months after irradiation and coincides with persistent DNA damage, which quickly impairs stem cell proliferation and survival [24].

Radiation's gastrointestinal injury: clinical and pathological manifestations

Radiation-induced gastrointestinal (GI) harm may manifest as symptoms or after treatment. The most notable signs of acute GI toxicity are stomach and rectal pain, nausea/vomiting, diarrhoea, more frequent stools, decreased food intake, and fluid and electrolyte loss. Typically, 3–4 months after the end of radiation exposure, chronic GI damage appears. Depending on the dose and volume of radiation exposure to the gut, the symptoms can include changes in bowel habits, diarrhoea, faecal incontinence, discomfort, and blood loss.

The base of the Lieberkuhn crypts includes numerous stem and progenitor cell populations that support the intestinal epithelium's high rate of regeneration. Intestinal vasculature, epithelial stem cells, and stromal components including resident and infiltrating macrophages and mast cells all interact dynamically in the pathophysiology of GI damage. In the onset of the acute phase of the GI damage, microvascular injury, which is injury mediated by endothelial apoptosis, is a significant and early factor. Secondary enterocyte depletion, a break in the mucosal barrier, bacterial translocation, and gut structural damage are all caused by vascular ischemia. Intestinal damage is reduced and epithelium regeneration is sped up when anticoagulant drugs are administered during and after high dose radiation exposure. While the ulcerative phase is a manifestation of the depopulation of the epithelial crypt stem and progenitor cells, the characteristic of the early phase of GI injury is the activation of ROS and their potential to trigger transcription factors and pro-inflammatory cytokines.

Radiation's clinical and pathological symptoms lung damage

Pneumonitis and constant fibrosis have customarily been viewed as the two sub-conditions of radiation-actuated lung harm. Intense aggravation that shows up inside the initial three months of radiation openness is known as pneumonitis. It involves a gamble of serious pneumonic outcomes that could bring about respiratory misery and organ disappointment. Radiation-incited fibrosis, a deferred result of radiotherapy, can seem a long time to years after radiation therapy and progress to obliterative fibrosis, which debilitates breathing and brings down personal satisfaction. Steroids are regularly used to treat radiation pneumonitis. With a middle endurance of 45 days, a review investigation of 385 cellular breakdown in the lungs patients with lung injury after radiation found that 16 (4.2%) died from radiation pneumonitis or steroids-prompted sequelae. In common clinical use, the accessible treatments for radiation-prompted lung fibrosis are as yet fruitless.

The over the top development of collagen and other extracellular grid components brings about fibrosis. When initiated, the myofibroblast is a significant cell that intercedes fibrosis. As per mainstream thinking, myofibroblasts create from fibroblasts and other neighborhood tissue mesenchymal cells or by an epithelial /endothelial-mesenchymal progress among epithelium and endothelial cells. Myofibroblasts can likewise be gotten from the flowing fibroblast-like cells got from bone marrow immature microorganisms.

Constant oxidative pressure has been seen in illuminated lung tissue after radiotherapy in cellular breakdown in the lungs patients as well as in preclinical rat models of lung injury, as has been displayed with different tissues and organs that have been presented to radiation [29, 30]. Through the actuation of NADPH oxidase, it has been suggested that fiery cells are the principal wellspring of ROS in illuminated lung; in any case, non-provocative cells can likewise produce ROS. For example, my fibroblasts can make hydrogen peroxide, which can cause the demise of epithelial cells [32]. Fiery cytokines, exorbitant ROS age, and the attack of bone marrow-determined stem and begetters cells into the injured tissue all consolidate progressively to cause ongoing late results of lung injury.

Radiation's clinical and pathological symptoms brain damage

There are three categories of clinical responses to radiation to the brain: acute, early delayed and late delayed effects. Acute effects are defined by indicators of elevated intracranial pressure, tiredness, and dizziness and occur during and/or shortly after the radiation exposure. The Blood Brain Barrior (BBB) disruption and edema are thought to be the primary causes of the acute effects. Early delayed effects, which appear 6–12 weeks after irradiation and are typically characterized by reversible symptoms like generalised weakness and somnolence and partly brought on by a temporary demyelination, are common. But it's the aftereffects that could have serious, irreversible brain effects. Clinical consequences of late brain injury can include brain parenchyma necrosis or cognitive impairments ranging from mild to severe. Late radiation necrosis can include specific neurological symptoms such seizures, cranial nerve dysfunction, and elevated intracranial pressure from prolonged vasogenic edema brought on by BBB destruction. MRI can be used to identify late radiation-induced white matter necrosis, which shows up as diffuse, non-specific alterations in the white matter.

Smaller incremental exposures of the normal tissue are frequently employed for clinical radiotherapy because the normal brain tissue tolerance is directly connected to the

volume and dose of tissues being treated. Estimating the volume of normal tissues exposed can be done with the use of the dose volume histogram. However, long-term functional alterations following whole brain radiation are common in adults and can be more obvious in young children, especially when radiation is applied when neural tissues are still developing. Childhood cancer survivors frequently experience late treatment-related impacts on neuroendocrine, cognitive, and learning abilities.

Deregulated proteins that are caused by IR but exclude repair foci and biases

Our aims to identify novel, potentially useful markers on protein levels that are related to radio sensitivity in addition to repair foci proteins. We included both considerably deregulated and not deregulated proteins in Supplementary Information 5 to give the reader a rich reflection of the evidence. Comparatively little research has been published on this subject within the set inclusion criteria (especially the correlation to radio sensitivity). Therefore, regardless of whether the results directly correlated with radio sensitivity, the study was included in the synthesis if the research contained tests that illustrate cell survival.

Conclusion

Known radiation hypersensitivity syndromes, such as Ataxia-Telangiectasia (A-T), Fanconi anaemia (FA), or Nijmegen Breakage Syndrome (NBS), can be blamed for the severe reactions in a limited percentage of individuals [11, 12, 13]. Children with A-T mutations have passed away after RT as recently reported [14]. However, only 1% of the patients exhibiting severe side effects had these hereditary abnormalities [15], and the majority of the augmented tissue reactions cannot be accounted for by known genetic illnesses.

Both candidate gene techniques and genome-wide association studies in radiation patients have offered some additional genetic correlations. Only a limited percentage of radiosensitive people could be found, [16]. Additionally, functional experiments that have been characterized as radio sensitivity predictors include DNA double stand break repair, production of chromosomal abnormalities, and radiation-induced apoptosis in ex vivo irradiated blood cells [17]. A significant amount of IR-induced transcriptional and translational changes were documented concurrently [18]. The cost-effective measurement of various possibilities, including posttranslational modifications of proteins, is made possible by recent technology advancements in omics applications, which is advantageous for these investigations. The probable link between IR-induced deregulation and radio sensitivity is being discussed for the majority of the candidates.

This paper's goal is to present the current state of our understanding of IR-induced alterations in protein expression in normal tissue that are associated to radio sensitivity. We concentrate on proteins and protein modifications because they may more accurately capture the real cell state, including stress responses, than transcriptome changes do because of posttranscriptional regulatory mechanisms [19]. Establishing protein biomarkers for the detection of radiosensitive or radio resistant individuals will subsequently be the next step. By identifying and safeguarding people who are occupationally exposed to radiation, this will help to personalize treatment methods to cancer patients during RT or help to facilitate a personalized risk assessment process.

Understanding the proteome landscape of healthy tissues is crucial first. Divergent baseline protein expression is present in various tissues and cell types. The majority of research concentrates on changes in blood or blood cells, while normal tissue reaction following IR is complex and depends on the kind of tissue. Therefore, further mechanistic research is needed to pinpoint how proteins affect radio sensitivity differently depending on the tissue. Because new advancements in radiation, including ultra-high dose radiotherapy (FLASH), use considerably higher dose rates that may influence radio sensitivity differently, the validation of proteins for varied dose rates will be a crucial topic in future studies.

Second, it can be challenging to characterize each predictor's total influence because numerous risk variables can affect how the body reacts to radiation. This section lists some of the variables that affect radio sensitivity and make it difficult to find a biomarker that can be used everywhere.

Numerous inherited hyper-radiosensitive diseases are recognized, and they are frequently caused by severe abnormalities in DNA repair genes. All fall under the umbrella of XCIND syndromes, which are distinguished by specific X-ray hypersensitivity, cancer susceptibility, immunodeficiency, neurological abnormalities, and double-strand DNA damage. Ataxia telangiectasia, Fanconi anaemia, Ligase IV syndrome, Radiosensitivity, Immunodeficiency, Dysmorphic Features, and Learning Difficulties (RIDDLE) syndrome, or ataxia telangiectasia and Rad3-related protein (ATR)-Seckel syndrome are a few examples of these diseases [15, 7, 9, 19]. Genetically defined radio sensitivity will be influenced by polymorphic polymorphisms, as well as mutations in numerous genes that result in the same or different DNA damage response pathways.

The findings from the International Commission on Radiological Protection (ICRP) and Advisory Group on Ionizing Radiation (UK) support the notion that there is strong evidence that not all people share the same radiation-induced risk of severe health outcomes. When common markers in at least two investigations were taken into consideration, we found only a small number of IR-induced proteins (H2AX, TP53BP1, VEGF, CASP3, CDKN2A, IL-6, and IL-1B) that associated to radio sensitivity. This is likely because radio sensitivity is a complicated trait. To find biomarkers that accurately identify radiation sensitivity, more research should be done on these prospective proteins and their potential interaction partners.

The MELODI platform emphasises the importance of finding biomarkers for disease susceptibility or radiation-related risks in individuals or population groupings. Individualized cancer care would not only assist patients, but it would also improve the effectiveness of the protection of those who are at risk due to occupational exposure. This comprehensive analysis emphasises the dearth of basic research focusing on normal tissue as opposed to tumour tissues. To investigate the function of particular proteins in various normal tissues, more research based on functional tests is required. Additionally, the requirement for using large cohorts, extremely sensitive methodologies for the search for biomarkers, as well as a focus on functional assessments of putative indicators in various accessible normal tissue, is strengthened by the frequent statistically

underpowered research (lymphocytes, fibroblasts, keratinocytes, and body fluids).

References

1. Rosenblatt E, Izewska J, Anacak Y, Pynda Y, Scalliet P, Boniol M, *et al*. Radiotherapy capacity in European countries: An analysis of the Directory of Radiotherapy Centres (DIRAC) database. Lancet Oncol. 2013;14:e79-e86.
2. Fazel R, Gerber TC, Balter S, Brenner DJ, Carr JJ, Cerqueira MD, *et al*. Approaches to enhancing radiation safety in cardiovascular imaging: A scientific statement from the American Heart Association. Circulation. 2014;130:1730-1748.
3. Salomaa S, Jung T. Roadmap for research on individual radio sensitivity and radio susceptibility-The MELODI view on research needs. Int. J Radiat. Biol. 2020;96:277-279.
4. Gomolka M, Blyth B, Bourguignon M, Badie C, Schmitz A, Talbot C, *et al*. Potential screening assays for individual radiation sensitivity and susceptibility and their current validation state. Int. J Radiat. Biol. 2019;96;280-296.
5. Wojcik A, Bouffler S, Hauptmann M, Rajaraman P. Considerations on the use of the terms radio sensitivity and radio susceptibility. J Radiol. Prot. 2018;38:N25-N29.
6. Otsuka S, Coderre JA, Micca PL, *et al*. Depletion of neural precursor cells after local brain irradiation is due to radiation dose to the parenchyma, not the vasculature. Radiat Res. 2006;165:582-591, PMID: 16669713.
7. Schuller BW, Binns PJ, Riley KJ, Ma L, Hawthorne MF, Coderre JA. Selective irradiation of the vascular endothelium has no effect on the survival of murine intestinal crypt stem cells. Proc. Natl. Acad. Sci. U S A. 2006;103:3787-3792, PMID: 16505359.
8. Schuller BW, Rogers AB, Cormier KS, *et al*. No significant endothelial apoptosis in the radiation-induced gastrointestinal syndrome. Int J Radiat Oncol Biol Phys. 2007;68:205-210, PMID: 17448874.
9. Rhee SG, Chae HZ, Kim K. Peroxiredoxins: a historical overview and speculative preview of novel mechanisms and emerging concepts in cell signaling. Free Radic Biol Med. 2005;38:1543-1552, PMID: 15917183.
10. Ehrhart EJ, Segarini P, Tsang ML, Carroll AG, Barcellos-Hoff MH. Latent transforming growth factor beta1 activation in situ: quantitative and functional evidence after low-dose gamma-irradiation. FASEB J. 1997;11:991-1002. PMID: 9337152.
11. 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. 2000;47:277-290, PMID: 10802350.
12. Anscher MS, Marks LB, Shafman TD, *et al*. Risk of long-term complications after TFG-beta1-guided very-high-dose thoracic radiotherapy. Int. J Radiat Oncol Biol. Phys 2003;56:988-995. PMID: 12829134.
13. Flanders KC, Sullivan CD, Fujii M, *et al*. Mice lacking Smad3 are protected against cutaneous injury induced by ionizing radiation. Am J Pathol. 2002;160:1057-1068, PMID: 11891202.
14. Vasireddy RS, Sprung CN, Cempaka NL, Chao M, McKay MJ. H2AX phosphorylation screen of cells from radiosensitive cancer patients reveals a novel DNA double-strand break repair cellular phenotype. Br. J. Cancer. 2010;102:1511-1518.
15. Bourton EC, Plowman PN, Smith D, Arlett CF, Parris CN. Prolonged expression of the gamma-H2AX DNA repair biomarker correlates with excess acute and chronic toxicity from radiotherapy treatment. Int. J Cancer. 2011;129:2928-2934.
16. Mumbrekar KD, Fernandes DJ, Goutham HV, Sharan K, Vadhiraja BM, Satyamoorthy K, *et al*. Influence of double-strand break repair on radiation therapy-induced acute skin reactions in breast cancer patients. Int. J. Radiat. Oncol. Biol. Phys. 2014;88:671-676.
17. Pouliliou SE, Lialiaris TS, Dimitriou T, Giatromanolaki A, Papazoglou D, Pappa A, *et al*. Survival Fraction at 2 Gy and gammaH2AX Expression Kinetics in Peripheral Blood Lymphocytes From Cancer Patients: Relationship With Acute Radiation-Induced Toxicities. Int. J Radiat. Oncol. Biol. Phys. 2015;92:667-674.
18. Lobachevsky P, Leong T, Daly P, Smith J, Best N, Tomaszewski J, *et al*. Compromized DNA repair as a basis for identification of cancer radiotherapy patients with extreme radio sensitivity. Cancer Lett. 2016;383:212–219.
19. Buchbinder D, Smith MJ, Kawahara M, Cowan MJ, Buzby JS, Abraham RS. Application of a radio sensitivity flow assay in a patient with DNA ligase 4 deficiency. Blood Adv. 2018;2:1828-s1832.
20. COPERNIC Project Investigators; Granzotto, A.; Benadjaoud, M.A.; Vogin, G.; Devic, C.; Ferlazzo, M.L.; Bodgi, L.; Pereira, S.; Sonzogni, L.; Forcheron, F.; *et al*. Influence of Nucleoshuttling of the ATM Protein in the Healthy Tissues Response to Radiation Therapy: Toward a Molecular Classification of Human Radio sensitivity. Int. J Radiat. Oncol. Biol. Phys. 2016;94:450-460.