Radiation Physics and Chemistry ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Radiation Physics and Chemistry

journal homepage: www.elsevier.com/locate/radphyschem

Towards evaluating post-irradiation tissue alterations

Eman Daar [a,b,*], D.A. Bradley [b], M. Alkhorayef [b,c], K.S. Al-Mugren [d], R.G. Abdallat [e], H. Al-Dousari [f]

[a] Department of Physics, Faculty of Science, The University of Jordan, Amman 11942, Jordan
[b] Department of Physics, University of Surrey, Guildford GU2 7XH, United Kingdom
[c] Department of Radiological Sciences, College of Applied Medical Sciences, King Saud University, PO Box 10219, Riyadh 11433, Saudi Arabia
[d] Department of Physics, Faculty of Science, Princess Nourah Bint Abdul Rahman University, Riyadh, Saudi Arabia
[e] Department of Biomedical Engineering, Faculty of Engineering, The Hashemite University, Zarqa, Jordan
[f] Jaber Al Ahmad Center for Nuclear Medicine and Molecular Imaging, Sulibekhat 1300, Kuwait

HIGHLIGHTS

- The effects of radiation on extracellular matrix and organised tissues are reviewed.
- Challenges in obtaining meaningful results are noted.
- Possible effects of recovery of tissues post-irradiation are unknown.

ARTICLE INFO

Article history:
Received 24 October 2015
Received in revised form
7 January 2016
Accepted 15 January 2016

Keywords:
Irradiation
Extra cellular matrix
Tissues

ABSTRACT

There is apaucity of data concerning irradiation effects on the extracellular matrix and on organised tissues. Examples of such research are cited as are some of the limiting factors towards obtaining meaningful results. This would engender a range of research towards further improving the quality of life, most pointedly of those receiving radiotherapy. As cancer survivor rates increase, survivors are more likely to experience side effects of radiotherapy. This study examines the effects of radiotherapy doses on the extracellular matrix as hyaluronic acid (HA) and pericardium.

1. Introduction

Not long after the discovery of X-rays it was recognised that tissue effects can occur as a result of irradiation. Most notably, this was of early as opposed to late changes in tissue properties, as in the observation of skin erythema first recognised at relatively high-doses received from soft X-rays, the severity of reddening increasing with dose. Indeed, the observation of the occurrence of skin erythema was soon to be followed by if not the first, then at least one of the earliest means of measuring dose, with the degree of reddening equated with dose through the so-called skin-erythema dose (SED). By the very early 1920s it had become more than apparent that X-ray exposures were producing a range of effects, including opacification of the lens of the eye (cataract formation) and of even greater alarm, malignancy; see for instance, the widely recorded developments leading to the X-ray Martyrs and to the first controls on radiation exposures. It would of course be unacceptable nowadays and indeed proscribed within any modern radiation controls legislation to knowingly produce such detrimental effects in an individual, other than for the purpose of producing net benefit for the individual, as for instance would typically be expected to be obtained in medical practice in which the net benefit should far outweigh the risks.

The safe, optimal use of radiation for the benefit of mankind has advanced considerably since those first very tentative steps, and with widening exploitation of radiation methods there now exist a wide range of fundamental studies aimed at providing strong underpinning knowledge of radiation effects on living tissues. These include both studies at the intracellular level (with which this article will not concern itself, not least because of the massive range of studies already devoted to the areas of such endeavour) as well as of extracellular effects, the latter including the extracellular matrix (ECM). As an example of the latter, interest has been shown in changes in protein structure, starting with

* Corresponding author at: Department of Physics, The University of Jordan, Amman 11942, Jordan.
E-mail address: e.daar@surrey.ac.uk (E. Daar).

http://dx.doi.org/10.1016/j.radphyschem.2016.01.025
0969-806X/© 2016 Published by Elsevier Ltd.

investigations using high-doses of radiation up to about 1 MGy, such as the work of Cassel in 1959, reported by Bailey (1968).

At such high-doses, as above, it is of no surprise that one could detect these extracellular changes even given the instrumentation capabilities available at that time. However, the sensitivity of instrumentation for ECM and organised tissue changes occurring at doses of clinical interest is rather more challenging. Confronting this challenge is one of the prime themes of the present review. This interest relates to the continuing desire to provide the most effective outcome for the patient while mitigating side-effects. Here note is made that while the aim of radiotherapy is to deliver the maximum radiation damage to tumour cells, damage can occur to organs at risk (OAR), such as for instance the heart in breast radiotherapy. Epidemiological studies of patients receiving radiotherapy for the left breast have shown a significant increase in cardiovascular death (Taylor et al., 2006), albeit there being well-established practices for limiting dose to the tissues of the heart. In what follows we provide a review of efforts aimed at studying changes in the pericardium, the intention being that such efforts be regarded as a model system, on the basis of which other organised tissue effects can also be studied. Similarly a review is made of radiation induced effects in hyaluronic acid (HA), important throughout the body, not least in terms of its lubractive role.

Pericardium is a part of the heart, mainly made of collagen fibres and can show changes in its structure at doses as low as 3 Gy (Stewart et al., 2013). In studies using HA and collagen as models for effects of radiation on tissues (Daar et al., 2010a, 2010b, 2011). HA is prevalent between the two layers of the pericardium, offering smooth motion between the serous and visceral layers. It is also of course prevalent in the skin and in the space between the articulating bones of skeletal joints, offering similar lubricating roles (Laurent et al., 1995). The HA and the framework offered by the collagenous systems provide for support and stability of motion and changes in the mechanical properties of these can result from insults that include irradiation as well as disease processes. Using well controlled radiation doses allowed for the study of these tissue components as models for investigation of biomechanical changes in a variety of tissues, not only directly as a result of irradiation but also in examining associated functionality changes from disease-based deformations. It should be mentioned that most of the work cited herein concerns doses at radiotherapy levels, an exception being food studies wherein the work also concerns viscosity changes, albeit at much higher doses (up to 10 kGy). Previous work (Daar et al., 2010a, 2010b) had collected a favourable degree of citations, Table 1 indicating the prime drivers of those referencing present studies.

2. Rheological studies

Given irradiation to a sufficient dose, changes can be observed in the viscosity of the HA that forms the basis of synovial fluid (being one example of ECM). As an aside it can be noted that HA is a non-Newtonian fluid, in particular showing dependency upon shear rate. Changes in the viscosity of HA can be explained in terms of depolymerisation and polymerisation, as previously investigated (Daar et al., 2010a, 2010b), use being made of rotating viscometers to alter shear rate. The rotating viscometer as well as the falling sphere method represent particular forms of instrumentation that enables measurement of the effects of irradiation on the structure of HA and of other proteins.The importance of this work is also clearly seen in measuring the side effects of irradiation of sensitive structures such as the rectum in prostate radiotherapy, pericardium effects in regard to left breast radiotherapy or indeed even in studies of the viscosity of food sauces, as seen in Table 1. HA is found to be in all body fluids and organs, as in for instance in the vitreous humour, synovial fluid of the joints, umbilical cord, and skin (Chen and Abatangelo, 1999). Table 2 shows the concentration of HA in some tissues and tissue fluids. One of the distinctive properties of HA is its high-molecular weight and therefore high-viscosity, making it a crucial element of the extracellular matrix (Bailey, 1968).

3. Irradiation effects on HA

The focus here is on HA as the synovial fluid of articulating joints, with HA forming a major component of this fluid, playing the dominant role in joint lubrication. In particular, studies have shown HA to be the major determinant of viscoelastic behaviour in synovial fluid (Laurent et al., 1995; Fam et al., 2007). It has been established that after typically the third decade of life the body will begin to lose the ability to produce HA, making it all the more important that irradiation changes in HA attract attention, particularly in regard to radiotherapy of the joints, with loss in viscosity and hence of wear resistance being expected to impact upon the quality of life.

In more detail, irradiation of HA will result in ionization and excitation of the atoms of HA and surrounding ECM, to the extent that this may lead to changes in the physical and chemical nature of the polymeric HA. Alterations can be a result of several effects, including simultaneous chain scission and cross-linking (Bailey, 1968; Buttafava et al., 2002) and bond deformation (Mohammed, 2008). Chain scissions will result in reduction of the molecular weight and the associated viscosity (Bailey, 1968). Conversely, cross-linking results in increasing viscosity, a reflection of increasing molecular weight. Since viscosity is an important property of the HA polymer, giving rise to its viscoelastic behaviour in the synovial joint, it is important to investigate this in regard to

Table 1
Prime drivers of research citing work reviewed herein.

Reference	Field of interest	Study purpose
Daar et. al., 2011	Breast radiotherapy	Pericardial stress–strain
Hatiboglu et al., 2012	Prostate radiotherapy	HA degradation
Noyes et al., 2012	Rectal dose as a result of prostate radiotherapy	Dose reduction through collagen injection
Song et al., 2013	Rectal dose as a result of prostate radiotherapy	HA sensitivity
Nguyen et al., 2013	Rectal dose as a result of prostate radiotherapy	HA degradation
Daar et al., 2010a, 2010b	Pericardium dose	HA degradation
Jonsson et al., 2012	Effect of radiation on HA expression	HA degradation
Bradley and Wells, 2013 and 2014 reprint	Biomedical applications reviewed: hot topics areas cited twice	HA and collagen changes
Akram et al., 2012	Biotechnology/effect of radiation on different sauces	Viscosity measurements
Tseng et al., 2013	Aortic valve	Viscoelastic properties
Chen and Abatangelo, 1999; Smeenk and van Lin, 2013	Prostate radiotherapy	HA degradation

Please cite this article as: Daar, E., et al., Towards evaluating post-irradiation tissue alterations. Radiat. Phys. Chem. (2016), http://dx.doi.org/10.1016/j.radphyschem.2016.01.025