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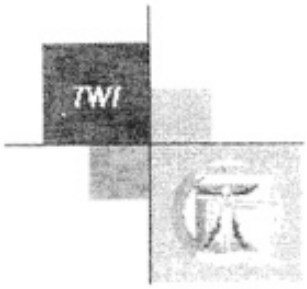

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Radio-immunological mechanisms of anti-inflammatory treatment: is there a way from the past into the future?

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Abstract
The anti-inflammatory efficiency of low-dose radiotherapy (LD-RT) for degenerative joint disorders was demonstrated over decades but had no explanation on a cellular or molecular level. As inflammatory diseases are the results of complex and pathologically unbalanced cellular and molecular interactions more recent in-vivo and in-vitro data will be discussed for possible explanation of the mechanism underlying ant-inflammatory LD-RT.2

Keywords: *LD-RT, anti-inflammation*

The maintenance of the integrity of a complex organism is a prerequisite of life and the exclusive achievement of the immune system. It has to distinguish between danger and non-danger, and, subsequently, has to reliably eliminate any unwanted target. The clinical appearance of this defense mechanism is inflammation, a basic biological process that is definitely able to destroy, depending on its activity and duration. Inflammation is a highly regulated process that necessitates the recognition of a foreign Ag, and the spatial limitation of the immune response. A lack of these regulatory factors leads to autoimmunity, SIRS or chronic inflammation, respectively. Any of these conditions represent major challenges in medicine, evoking substantial needs for efficient anti-inflammatory treatments.

As early as 1898, Sokoloff [1] treated painful joint disorders successfully with LD-RT developing into the anti-inflammatory treatment of choice for decades until, in 1965, an increased mortality from leukaemia and aplastic anaemia after LD-RT of patients with ankylosing spondylitis was reported [2]. Due to this observation and improvement of anti-inflammatory drugs, like steroids or non-steroidal anti-inflammatory drugs (NSAID), medication increasingly dominated the field. Towards the end of the past century, NSAID counted among the most frequently consumed drugs, when increasing knowledge, coming up with an evidence-based medicine, revealed 10,000s of deaths worldwide from gastrointestinal bleeding and myocardial infarction [3,4] and considerable number of non-responders, leading to a revival of interest in low-dose radiotherapy (LD-RT).

This era witnessed an unprecedented eruption of immunologic knowledge that led to a growing understanding of the inflammatory process and its constituents like Ag recognition, intercellular signalling, and systemic regulation through apoptosis and necrosis. Prostaglandin E2 (PGE2) was found responsible for swelling, erythema, heating and pain, all subject to PGE2-mediated vessel dilatation and permeability, and nociceptor stimulation. Thus, the inhibition of COX2, a tissue-borne enzyme producing PGE2, by NSAID is effective. Inactive COX2 is present in practically any tissue and is activated by pro-inflammatory cytokines, predominantly IL-1β or IL-6.

Cytokines serve regulatory functions in the inflammation network by (de-)activating enzymes or immunocompetent cells including their own producers via feedback mechanisms. In this decade, proinflammatory cytokines can be targeted by moAb

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or receptor fusion proteins, blocking downstream induction of COX2 and ameliorating inflammation. The interaction between cells involved in the immunoregulatory network can today be influenced by substances interfering with several cellular targets.

While the action of drugs on the inflammatory process was well understood, LD-RT efficacy had no explanation on a cellular or molecular level. First radiobiologic research was to create experimental evidence for the longstanding clinical experience. In 1986 Budras et al. [5] reported on LD-RT in an animal model of acute arthritis, resulting in a decrease of joint swelling. The efficacy of LD-RT in acute local inflammation was independently confirmed [6,7] and evidence in chronic local inflammation [8] and systemic inflammation [9] followed. Secondly, research dealt with the influence of LD-RT on the inflammatory casacade. The adhesion of peripheral blood mononuclear cells (PBMC) to EC as initial step of tissue inflammation was decreased [10–12]. After LD-RT expression by EC of TGF-β1, known to downregulate leukocyte adhesion, was increased on mRNA and protein level, and anti-TGF-β1 Ab treatment restored adhesion of PBMC to irradiated EC [12,13]. *In vitro*, apoptotic cells exert immunoregulatory effects by switching the cytokine profile of neighbouring MΦ to an anti-inflammatory phenotype with induction of IL-10 and reduction of TNF-α [14]. Irradiation induces a dose-dependent progression of apoptosis in PBMC *in vitro* with a remarkable relative maximum in the dose range of LD-RT [15,16] and a corresponding relative maximum and minimum of IL-10 and TNF-α secretion [17]. Early apoptotic leukocytes proteolytically shed adhesion molecules from their surfaces [18]. Intracellular effects of LD-RT on granulomatous tissue were decreased the expression of iNOS, and increased the expression of haemoxigenase-1 and HSP-70 [8]. In granulocytes, LD-RT induces a relative maximum of total Akt coinciding with induction of apoptosis [16]. Various transcription factors such as NF-κB, c-fos or c-jun, that collectively form homo- or hetero-dimeric AP-1 transcription factor complexes, are of crucial importance for the expression of the inflammatory effector molecules. In EC, LD-RT induces a relative maximum of NF-κB transscriptional activity and AP-1 activation [19,20].

Thirdly, recent research translated many of the *in vitro* results into a mouse model. LD-RT prior to induction of inflammation attenuated TGF-β1-mediated leukocte adhesion to intestinal venules [9]. In primarily inflammation-bound TNF-α transgenic mice, resembling the clinical situation of rheumatoid arthritis (RA), LD-RT applied in an early stage temporarily ameliorated signs and symptoms of the disease [21]. Most experimental anti-inflammatory effects display a relative maximum between 0.3 and 1.0 Gy, which is exactly the dose range where the vast majority of excellent clinical experience with LD-RT has been gathered over more than one century.

Despite all historical clinical experience and new immunology based insights in the mechanisms of action, there is an obvious lack of high level evidence derived from well designed randomised controlled trials (RCT) for LD-RT. Pharmacological interventions are based on excellent evidence, comprising thousands and thousands of patient years, both concerning efficacy and safety. It has always been the primary task of the physician to balance risks and benefits of a treatment and its alternatives. Yet, in anti-inflammatory therapies, this is hard to achieve, especially with view to final endpoints such as death. We do not know what the exact risk of LD-RT is today when it is applied in a localised and controlled way. And, we certainly have to reconsider NSAID in the light of today's evidence for lethal gastrointestinal bleeding and cardiovascular events. But with the knowledge available, it seems to be time to accept LD-RT as an alternative in cases refractory to medication or with individual risk profiles not fitting with NSAID, i.e. older patients with considerable gastrointestinal or cardiovascular risks.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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