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Review

Clinical perspectives of cancer stem cell research in radiation oncology

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ABSTRACT

Radiotherapy has a proven potential to eradicate cancer stem cells which is reflected by its curative potential in many cancer types. Considerable progress has been made in identification and biological characterisation of cancer stem cells during the past years. Recent biological findings indicate significant inter- and intratumoural and functional heterogeneity of cancer stem cells and lead to more complex models which have potential implications for radiobiology and radiotherapy. Clinical evidence is emerging that biomarkers of cancer stem cells may be prognostic for the outcome of radiotherapy in some tumour entities. Perspectives of cancer stem cell based research for radiotherapy reviewed here include their radioresistance compared to the mass of non-cancer stem cells which form the bulk of all tumour cells, implications for image- and non-image based predictive bio-assays of the outcome of radiotherapy and a combination of novel systemic treatments with radiotherapy.

Considerable progress has been made in the identification and biological characterisation of cancer stem cells during the past years. Cancer stem cells (CSC) have been defined by Clarke and colleagues as a small subpopulation within a tumour that possesses the capacity of self-renewal and to cause the heterogeneous lineages of cancer cells that comprise the tumour [1]. These cells have the ability to sustain tumour growth. From a clinical point of view, this means that a patient suffering from cancer can only be cured if all CSCs are eliminated by the treatment and/or anti-tumour response mechanisms of the patient [1–3].

The implications of the CSC concept for radiobiology and radiotherapy have recently been reviewed [2,4–6] and will only briefly be summarised in the present article. Here we will address the question whether results of CSC related research are suitable to explain preclinical-translational and clinical data supporting that the outcome of radiooncological treatments depends on CSC. As very recent biological findings lead to more complex models of CSC we will also discuss the potential implications of these refined models in radiotherapy.

Inactivation of CSC determines permanent local control after radiotherapy

If all CSCs are inactivated, permanent local tumour control is achieved by radiotherapy. In contrast, if one or more CSCs survive irradiation, are not eliminated by or from the host organism or are acquiring a permanently dormant state, recurrent tumour will result. Therefore local tumour control assays, that is the evaluation of the rate of permanent local control achieved after different doses and treatments, functionally tests the effect of irradiation on CSC, as reviewed in [2]. Typically, local tumour control increases as a sigmoid function with increasing biological effective dose (Fig. 1a), which can be explained by exponential CSC kill and the Poisson statistics [2,7]. This concept is supported by exponential inactivation of cells by radiation, by a wealth of preclinical and clinical data demonstrating sigmoid dose–response relationships for tumours and by experimental data correlating tumour cell survival after irradiation ex vivo, in vitro or in vivo with tumour control probability [2,8]. In line with the concept of CSC, comparison of quantitative tumour transplantation- with local tumour control assays shows an inverse log-linear correlation [9]. Furthermore the dose necessary for local tumour control increases with the logarithm of (viable) tumour volume which is in line with an exponential cell kill by radiation and the assumption that the number of CSC correlates linearly with the tumour volume [2,4,10].

It is important to note that radiobiological mechanisms of tumour resistance which have been derived from preclinical or clinical studies using local tumour control as the endpoint including repopulation during treatment, impact of hypoxia or other parameters of the tumour micromilieu, and the effect of drugs on tumour control after irradiation all reflect their respective effect on CSC survival [2,4]. Another important finding is that results obtained from radiobiological or clinical research using local tumour control as the endpoint may dissociate from volume-related endpoints, e.g. tumour regression or growth delay, as these reflect the effect of radiation on the bulk of tumour cells *cf* [11–13]. Several preclinical studies have shown that combining radiotherapy with drugs may

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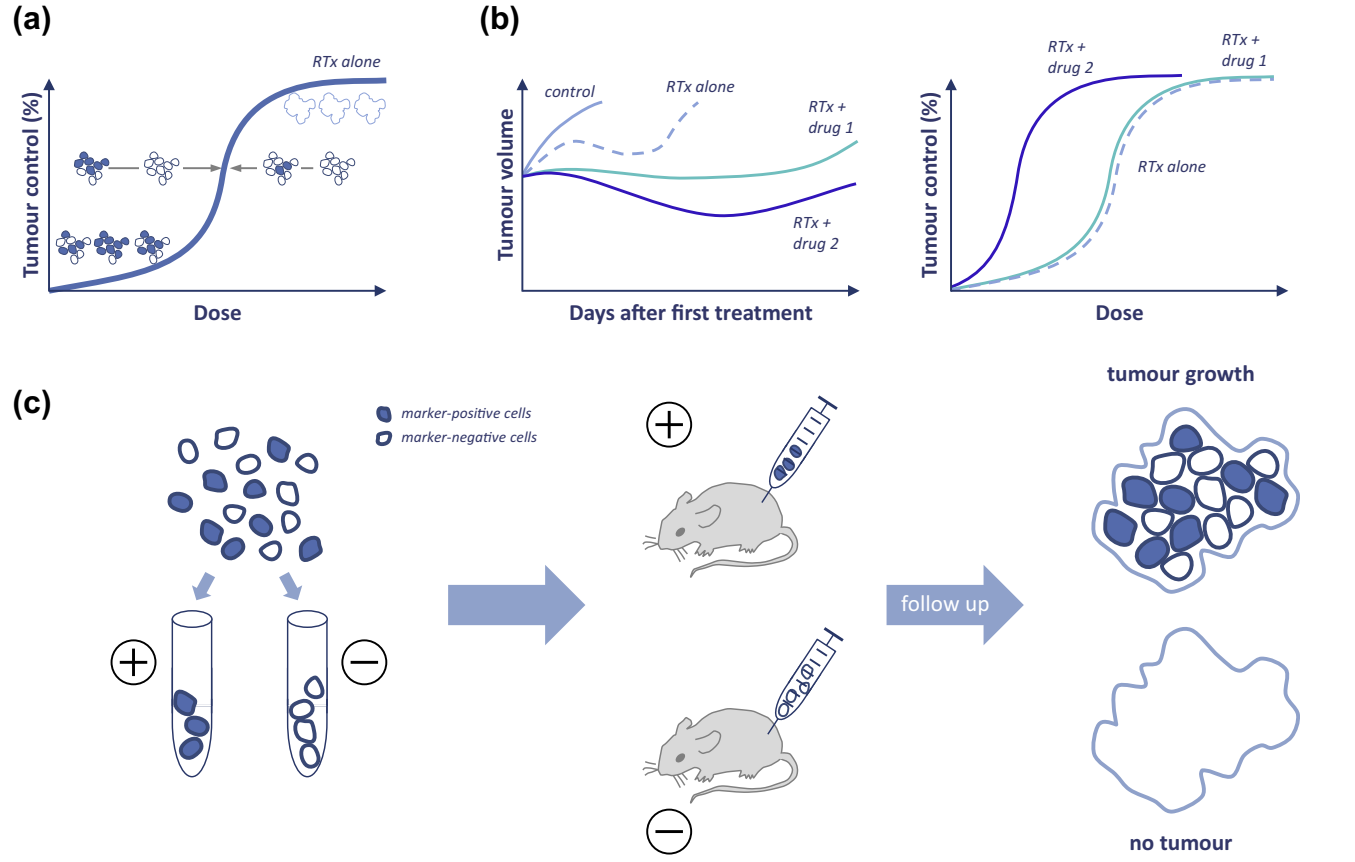

Fig. 1. Local tumour control increases as a sigmoid function with increasing irradiation dose, which can be explained by exponential CSC kill and Poisson statistics (a). The combination of radiotherapy with drugs may significantly enhance tumour regression or growth delay without improving local tumour control (drug 1) or with enhanced local tumour control (drug 2). Currently only local tumour control assays functionally test the effect of irradiation or combined modality treatments on CSC (b). In order to evaluate stem cell characteristics of marker-positive cells compared to marker-negative cells in vivo transplantation assays are used (c).

significantly enhance tumour regression or growth delay without improving local tumour control *cf* [12,13]. Thus, in order to assess the curative potential of radiotherapy or combined modality treatment, tumour control assays should be used whenever possible (Fig. 1b).

Identification of CSC

Classical radiobiological approaches have identified CSC by transplantation- or metastases forming-assays in vivo [9,14–17]. In addition CSC survival after irradiation was determined by local tumour control assays (vide supra). These functional assays are of significant importance for investigating the radiobiological characteristics of CSC. However, these assays are not able to identify individual CSC in tumour cell samples, histological examinations or cell cultures. Enormous progress was achieved in the identification of CSC with the introduction of immunohistochemistry and flow sorting techniques, as reviewed in [8,18]. CSC and non-CSC are discriminated based on surface markers. Currently used markers associated with CSC characteristics include CD133, ALDH1, CD24, and CD44, many more are under investigation. In order to validate the stem cell characteristics of marker-positive cells quantitative transplantation assays are used (TD_{50} assays, i.e. the number of cells which is necessary to induce tumour growth in 50% of host animals; Fig. 1c). They show that often hundreds or thousands of marker-positive cells are necessary to reach tumour growth [8], suggesting that currently used markers accumulate CSC but not necessarily identify single CSC. This is supported by observations that even marker-negative cells can initiate tumours [19]. Further limitations of currently used CSC markers are reviewed in some more detail in *cf* [8] and a paper by Peitzsch et al. in this issue of this journal [20], supporting the need for the use of novel biotechnology in this field of research.

Clinical evidence that CSC impact outcome of radiotherapy

As outlined above an increase of the tumour control dose with the logarithm of the number of CSC is expected from radiobiological reasoning. As a first approximation the number of CSC should increase linearly with increasing tumour volume. Indeed correlation of local tumour control dose and the logarithm of tumour volume has been observed in a range of preclinical experiments [4,5,10,21–23] and in several clinical studies in a number of tumour entities [24–29] (Fig. 2a). The proportion of tumour-initiating cells among all tumour cells has been shown to be highly variable between individual tumours or individual tumour lines even if originating from the same clinical entity [2,4,9,14–17]. From this it is expected that determination of the CSC density in individual tumours adds predictive power to the estimation of the number of CSC in individual tumours beyond the determination of tumour volume [6] (Fig. 2a). Research on several tumour types has addressed whether biomarkers of CSC density correlate with the outcome of radiotherapy (Table 1).

Glioblastoma

In xenograft transplantation assays CD133-positive brain tumour cells have been shown to initiate tumour growth whereas the injection of marker-negative cells did not cause a tumour [17]. Bao et al. showed that CD133-expressing glioma cells, considered

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