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LETTERS TO THE EDITOR

Particle species dependence of cell survival RBE: Evident and not negligible

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To the Editor,

With great interest we noticed the work of Singers Sørensen, Overgaard and Bassler [1], where the authors question if the linear energy transfer (LET) of ion beams can serve as a unique parameter determining the relative biological effectiveness (RBE) of ion irradiation, neglecting the particular particle species. For this purpose the authors collected a set of in vitro cell survival data from the published literature and came to the conclusion that 'the influence of varying the particle type on the RBE was far from obvious, compared to the general experimental noise'. They further state in the abstract that '…a dependence of particle type cannot be concluded, and LET alone in fact does seem to be an adequate parameter for describing RBE at 10% survival'.

We agree that collecting in vitro cell survival data is the most convenient way to elucidate general systematics of the RBE. We also agree that fluctuations of RBE values as observed in the data are large. Moreover, it is obvious that for all ions for a given LET only a certain range of RBE values is assumed. However, the conclusions Sørensen et al. draw seem to be misleading and not consistent to us. By reanalyzing the data they used, a dependence of RBE on LET *and* particle species rather than LET alone is clearly evident, although it is partially shaded by larger RBE fluctuations. Using a purely LET dependent RBE estimate would in turn mean a systematic error in the RBE estimates. We show that such a simplification hence suggests implications for particle therapy, which are not acceptable with respect to clinical endpoints. We propose that neglecting the particle type dependence of RBE is only appropriate for having a first guess of possible RBE values instead of a reliable prediction. The use of treating LET as the only parameter determining the RBE is thus very limited.

Figure 1 shows RBE at 10% survival of V79 cells plotted against the LET for He, C and Ne ions. Data points were reproduced from figure 1d of [1], hence the present discussion is based on the same data as used by Sørensen et al. As the authors nicely demonstrated in this LET range the RBE-LET characteristics are in good agreement with a linear relationship (although at the high LET end of the plot this can be questioned for He, as in this region the RBE-LET maximum occurs). The solid lines are linear fits to each data set of He, C and Ne ions. A visual impression suggests: 1) that the data points

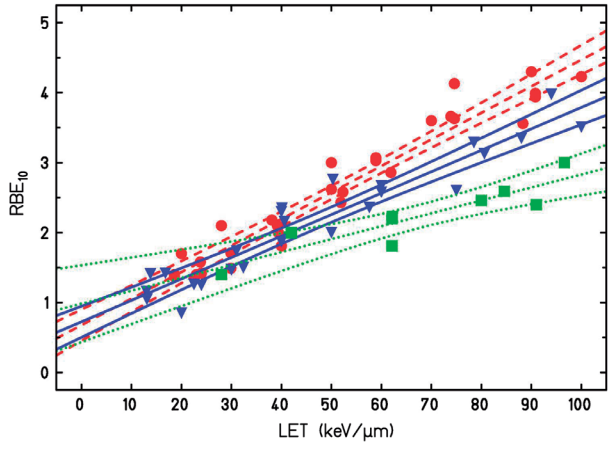

Figure 1. RBE_{10} vs. LET for He (red circles), carbon (blue triangles) and neon (green squares) ions for V79 cells as investigated in [1] along with three individual linear fit lines and boundaries of 95% confidence intervals of the mean values.

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Table I. Offset and slope parameters for the linear fits to He, C and Ne ion data as shown in Figure 1 and RBE_{10} values for an LET of 70 keV/μm. Uncertainty indications are standard errors and 95% confidence intervals of the fit parameters and standard deviations of the residuals for the RBE values.

	Offset	Slope (μm/keV)	RBE_{10} at 70 keV/μm
He	0.68 ± 0.11	0.038 ± 0.002	3.33 ± 0.25
	[0.453; 0.900]	[0.0341; 0.0418]	
C	0.73 ± 0.11	0.031 ± 0.002	2.87 ± 0.26
	[0.502; 0.947]	[0.0265; 0.0348]	
Ne	0.98 ± 0.23	0.019 ± 0.003	2.28 ± 0.20
	[0.435; 1.533]	[0.0107; 0.0262]	

corresponding to He, C and Ne ions cover different regions in the plot (red points usually lie above the blue ones, which in turn are superior to green ones); 2) that the slopes corresponding to the three ion types are different; 3) that the sets of data points corresponding to each ion type overlap partially, but are spatially well separated in particular for higher LET; and 4) that the fluctuation of the data points form hypothetical uncertainty bands around the fitted lines which do not overlap at LET values between 50 and 100 keV/μm.

For a more quantitative analysis in Table I we list the offset and slope fit parameters of the best fit lines included in Figure 1 along with the standard errors of these parameters (which make up 68% confidence intervals) and the 95% confidence intervals. The latter indicate, that the three slopes indeed are significantly different, as the intervals for Ne and C do not overlap, and between C and He the overlap is very small. In Table I we also list the RBE_{10} values calculated by the linear fits for a LET of 70 keV/μm. The error of the RBE values is the standard deviation of the residuals, which were checked to be uniform, i.e. without systematic variations, for all LETs. Again it is obvious that the values are different. In Figure 1, the shown limit curves of uncertainty bands mark the 95% confidence region of the mean RBE values. For a confidence level of 68% this bands shrink even more (not shown) and are interpreted as standard error of the mean RBE values. While for low LET values there is significant overlap, for higher LETs due to the different slopes the overlapping decreases and above 80 keV/μm finally vanishes, i.e. the data points cover different regions in the plot. But also for lower values down to approximately 40 keV/μm, where overlap occurs, the values for the expectation values of RBE can be distinguished for the three ion species. This means that the stochastic limits of the RBEs are definitely distinguishable, though individual experiments may show RBE values in a converse way.

The relevance of this interpretation for particle therapy is a direct consequence: for a given tumor incidence and characterization (staging etc.) due to inter-individual differences in radiation sensitivity and radio response there will be an optimal total dose for each patient, which, however, is not known. Evaluation of clinical trials leads to recommended doses to be given, which are regarded as an average of the individual optimal doses. Failure of the regimen is then attributed to stochastic uncertainties only. For light ion therapy where the RBE is important, *any* systematic uncertainty in RBE will result in a systematic deviation from the recommended dose, therefore enhancing failure of the regimen when averaged over a patient population. As the dose response curves for clinical endpoints such as tumor control or normal tissue complications are quite sensitive on dose within the therapeutic window, even small changes in dose (resulting from neglecting particle type dependence of RBE) may lead to large changes of clinical results [2].

RBE as a function of dose, of the cell or tissue sensitivity to radiation, as well as of the particle species is well established on an empirical basis in many experiments [3], predictable by radiobiological models and to some extent also understood on a mechanistic level. In this framework it seems questionable if neglecting the particle type as an influential factor for RBE is really a simplification; at the same time relevant systematic shifts of RBE are induced, which even further enhance the uncertainties of RBE. We hence suggest that the simplification as proposed in [1] should not be applied in the field of radiobiology or radiotherapy.

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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