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CLINICAL & BASIC RESEARCH

A Logarithmic Formula to Describe the Relationship between the Increased Radiosensitivity at Low Doses and the Survival at 2 Gray

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معادلة لوغارتمية لوصف العلاقة بين زيادة الحساسية الإشعاعية عند الجرع المنخفضة والبقاء عند 2 غراي

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الملخص: الهدف: تتأثر الحساسية الاشعاعية داخلية المنشأ المستخدمة عند الجرع المعتمدة في العلاج الإشعاعي بفرط الحساسية الإشعاعية و زيادة المقاومة الإشعاعية (HRS/IRR)عند الجرع المنخفضة. يهدف هذا العمل الى استكشاف هذه العلاقة. **الطريقة:** تم تحليل منحنيات البقاء لثمانية عشر خط خلوي من خلايا الأورام البشرية و ذلك باستخدام نموذجين لعملية الملاءمة للنقاط العملية من أجل الحصول على المؤشرات الضرورية ذات العلاقة بهذه الدراسة. **النتائج:** يمكن وصف نسبة زيادة المقاومة الاشعاعية αs/αr مقابل البقاء عند 2 غراي بعلاقة لوغارتمية تؤدي إلى سلسة من المستقيمات. **الخلاصة:** العلاقة المستخلصة تبين وجود علاقة مباشرة بين فرط التحسس– زيادة المقاومة الإشعاعية والبقاء عند الجرع المعتمدة سريريا وهي 2 غراي.

مفتاح الكلمات: فرط التحسس، العلاج بالأشعة، خط خلوي، ورم، تحليل.

ABSTRACT: ***Objectives:*** Intrinsic radiosensitivity at doses used in radiotherapy is linked to hypersensitivity (HRS) and increased radio resistance (IRR) at low doses. The aim of this study was to explore this relationship. ***Methods***: Survival curves for 18 human tumour cell lines were analysed, using two models to fit the data points in order to extract the necessary parameters relevant for this study. ***Results***: The IRR ratio α_s/α_r *versus* the survival at 2 gray (Gy) can be described by a logarithmic relation which leads to a series of straight lines. ***Conclusion***: The relationship obtained implies that there is a direct link between HRS/IRR and survival at clinically relevant doses of 2 Gy.

Keywords: Hypersensitivity, radiotherapy; Cell Line; Tumor; Analysis.

Advances in Knowledge

- *For the first time, the relationship between the increased radio resistance (IRR) α_s/α_r and the survival at 2 gray (Gy) (SF2) has been described by a series of straight lines.*
- *This study uses the repairable-conditionally repairable (RCR) model for the first time to extract αs in addition to the inducible repair (IR) model, which is usually applied for this purpose.*
- *Since the RCR model is statistical in nature, special analysis had to be done in order to extract the hypersensitivity (HRS) parameters αs.*
- *To have good fits, the survival curve data points were separated into two parts. The hypersensitivity region part (<1 Gy) was fitted to the IR or the RCR model, and the conventional survival curve region (>1Gy with the 0 Gy point) was fitted to the linear quadratic model.*

Application to Patient Care

- *The influence of HRS/IRR on clinically relevant doses is of great importance in radiation therapy.*

Over the last two decades, much attention has been focused on the existence of a hypersensitivity region in the survival curves for many mammalian cells at doses below 0.5 gray (Gy). This makes the linear-quadratic (LQ) equation inappropriate for use at low doses. This phenomenon, termed hypersensitivity (HRS), precedes the occurrence of relative resistance per unit dose to cell killing by radiation over the dose range ~0.5–1 Gy. This latter phenomenon is increased radioresistance (IRR). The ratio of the initial slope of the survival curve associated with the hypersensitivity region (α_s) to the slope in the shoulder region (α_r) is usually

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used as a metric in the analysis of the HRS/IRR phenomenon. The HRS/IRR phenomenon has been found in different types of cell lines, both *in vivo* and *in vitro*. The former includes cell lines from plants, bacteria and mammals. The latter mostly involve human tumour cell lines.[1–5]

Many researchers have tried to explain this phenomenon depending on the analysis of cell phase or gene structure, while others have tried to study the influence of this phenomenon on dose fractionation in radiotherapy by analysing survival curve parameters.[1,6,8,10–14] Explanations of this phenomenon are still regarded as matters of controversy.

The use of mathematical equations to extract useful parameters to be applied in radiotherapy procedures is very important. In the case of HRS/IRR curves, there is always a need to establish a relation between α_s/α_r and the survival at 2 Gy (SF2), which is clinically relevant. Those attempting to develop a standard equation to be used in such a procedure have been faced with difficulties related to an inadequate or poorly fitting equation, colony assays being unreliable at low doses, and the difference in the new technology methods that are used to identify the position of the plated cells such as the fluorescence-activated cell sorting method (FACS) and the dynamic microscope image processing scanner method (DMIPS).[12]

In order to make it possible to fit the hypersensitivity survival curves to a model and extract useful parameters for the analysis, the LQ model was modified by Joiner and Johns.[15]
This new model, the inducible repair (IR) model, involves two new parameters in addition to α and β in the original LQ model. These parameters are α_s which is a measure of the initial slope in the low dose region and the D_c parameter which represents the dose at which the inflexion occurs from HRS to IRR. The α parameter in the LQ model, termed αr in this model, defines the slope in the shoulder region. The most common inducible repair (IR) model equation is given by:

$$S = \exp\left(-\alpha_r 1 + (\alpha / \alpha_r -) e^{-D/D_c}\right) D - \beta D^2)$$

[Equation 1]

where S is the survival fraction, D is the dose and α_s, α_r and D_c as defined above.[12] Equation 1 has been used extensively to fit the HRS/IRR curves, with varying goodness of fit results. Another equation based on statistical analysis has been put forward to describe HRS/IRR data. This equation does not give α_s and α_r directly. Consequently, it is not used as commonly in α_s/α_r analysis. The model that adopts this equation is called the repairable-conditionally repairable (RCR) model and is described by:

$$S(D) = e^{-aD} + bDe^{-cD}$$ [Equation 2][16]

To overcome some of the obstacles that prevent obtaining reliable values for α_s/α_r and for SF2 to be used in establishing the relationship between them, we have chosen to fit a set of survival curves that belong to human tumour cell lines to Equations 1 and 2 in order to obtain smooth curves that reasonably describe all survival data with the aim of finding a relation between α_s/α_r and SF2.

Methods

A set of 18 survival curves related to various kinds of human tumour cell lines were compiled from the literature.[7,17–25] Data points and their error bars were obtained using programming techniques described in previous work.[26] Each survival data set for a given cell line were fitted to the IR model and the RCR model using all data points on the curve. The fit results did not prove to be satisfactory in most cases. This was particularly evident in the case of the IR model. However, fits carried out using the HRS/IRR part of the survival curve produced acceptable results. This part is represented by the region of 0–1 Gy or slightly higher in very few cases. The other part of the survival curve (>1 Gy) together with the 0 Gy dose represents the conventional survival curve with no HRS/IRR region. This was fitted to the LQ equation. The criteria used for considering the fit acceptable involved having the fitted curve as close as possible to data points with small residuals values. In addition, the residuals distribution should be of the random type narrowly centred near zero. The fulfillment of these criteria was checked by having the sum of squares error (SSE) and the root mean square error (RMSE) being close to zero, and R^2 and the adjusted R^2 (AJR) are very close to 1.

A problem arises when handling cases with survival curves data points which are randomly distributed. These cannot be described by a smooth curve. Such cases are usually associated

Table 1: Best fits parameters from inducible repair, repairable-conditionally repairable and linear-quadratic models

Cell lines	Parameters obtained from best fits to the IR model			Derived parameters from best fits to the RCR model		Parameters obtained from best fits to the LQ model	
	α_r (Gy^{-1})	α_s (Gy^{-1})	D_c (Gy)	α_s (Gy^{-1})	D_c (Gy)	α (Gy^{-1})	SF2 derived
RT112 (18)	0.27 ± 0.00	1.07 ±0.21	0.29 ± 0.06	0.99	0.47	0.17 ± 0.50	0.62
AGS (19)	0.24 ± 0.00	1.30 ± 0.19	0.39 ± 0.07	1.19	0.5	0.42 ± 0.05	0.45
PC3 (19)	0.77 ± 0.00	0.68 ± 0.17	0.44 ± 0.12	0.66	0.51	0.27 ±0.07	0.52
T98G (20)	0.39 ±0.00	0.84 ±0.34	0.45 ± 0.29	0.74	0.56	0.15 ± 0.02	0.69
Be11 (7)	0.16 ± 0.00	1.37 ± 0.19	0.25 ± 0.04	1.294	0.39	0.16 ± 0.03	0.68
A549 (19)	0.82 ± 0.00	1.26 ± 1.32	0.16 ± 0.12	1.02	0.32	0.20 ± 0.06	0.71
BMG1 (21)	5	19.55 ± 7.36	0.08 ± 0.02	14.27	0.09	0.10 ± 0.10	0.81
DU145 (22)	0.38 ± 0.00	0.54 ± 0.19	0.32 ± 0.12	0.49	0.4	0.17 ± 0.01	0.64
T98G (17)	0.29 ± 0.00	1.28 ± 0.62	0.13 ± 0.04	0.89	0.18	0.08± 0.03	0.73
HT-29 (23)	0.21 ±0.00	0.98 ± 0.11	0.23 ± 0.02	0.88	0.28	0.07 ± 0.01	0.71
MeWo (23)	0.38 ± 0.00	1.00 ± 0.97	0.46 ± 0.68	0.83	0.63	0.25 ± 0.02	0.27
PECA4197 (21)	0.29 ± 0.00	4.61 ± 0.87	0.35 ± 0.06	4.16	0.32	0.12 ± 0.00	0.64
PECA4451 (21)	0.30 ± 0.00	2.93 ± 0.09	0.37 ± 0.12	2.63	0.38	0.40± 0.0624	0.65
BJ (24)	0.31 ± 0.00	1.28 ± 0.73	0.85 ± 0.50	1.18	1.1	0.28 ± 0.09	0.57
SCC-61 (25)	0.1 ± 0.00	1.41 ± 0.61	0.8 fixed	0.87	0.8	0.47 ± 0.09	0.30
SQ20B (25)	0.5 fixed	0.69 ± 0.21	0.63 ± 0.17	0.51	0.65	0.03 ± 0.01	0.88
U1 (22)	0.70 ± 0.00	0.18 ± 0.04	0.11 ± 0.02	0.061	0.32	0.001 ± 0.011	0.92
U87 (21)	0.20 ± 0.00	10.35 ± 3.06	0.22 ± 0.05	9.211	0.19	0.70 ± 0.40	0.57

IR = inducible repair; RCR = repairable-conditionally repairable; LQ = linear-quadratic; Gy = gray.

with small fractional doses arising from the difficulty in measuring small changes in survival. In these cases, the curve-fitting procedure becomes fruitless. In order to overcome this problem, some data treatment becomes necessary. The treatment employed involves constrained data smoothing. This is performed using the MATLAB library routine "smooth", which uses a successive averaging method. In addition, one constraint was added on the smoothing process. The constraint was that no smoothed data point was to move during the smoothing process beyond its error-bar boundaries. This process was similar to weighting the data points, but it was found that the smoothing method gave better results.

The other problem was that the RCR model is statistical in nature; thus, it does not give the required physical parameters directly as is the case with the the IR model. This problem was solved by finding the first derivative on the survival curve at the initial slope which represents α_s, and the first minimum value of the survival followed by increase of survival defined as D_c. The α parameter from the LQ fit was used as α_r. Whether one is using either the IR model or the RCR model, this treatment is considered justified since the IR model is not efficient enough to control the HRS/IRR region and the conventional part of the survival curve at the same time. The same argument applies in the case of the RCR model, which is better at describing the data than the former in spite of its statistical nature.

Results

The fitting results from the models IR, RCR, and LQ for various cell lines are shown in Table 1. The first column in Table 1 gives the cell lines. Columns 2, 3 and 4 represent the α_s, α_r and D_c parameters that were obtained by selecting the best fits to the region 0–1 Gy when using the IR model. Columns 5 and 6 represent the α_s and D_c parameters that were derived from the best fits to the RCR model

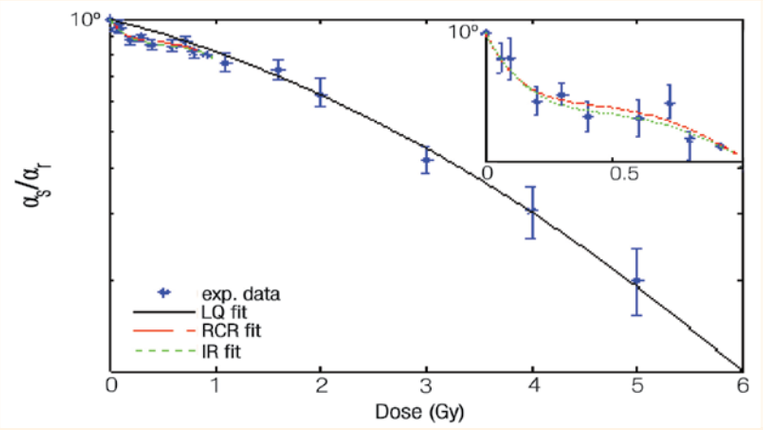

Figure 1. Survival curve fits for RT112 cell line to the LQ, IR, and RCR models.[18] The upper right figure is a magnified portion for IR and RCR fits in the hypersensitivity region.
LQ = linear-quadratic; RCR = repairable-conditionally repairable; IR = inducible repair; Gy = gray.

in the region of 0–1 Gy using the first derivative method mentioned above to obtain α_s and the first minimum point on the curve to get D_c. The last two columns in this table represent the α_r and the SF2 values that were obtained from fitting the survival curve data in the region >1 Gy together with the 0 Gy to the LQ model. Figure 1 shows an example of the fit for the three models for the cell line RT112.

When α_s/α_r against SF2 are plotted on a linear scale, the data points are distributed randomly. However, when the α_s/α_r for the best fit results from the RCR model and the LQ model are plotted on a logarithmic scale against SF2, the data points become grouped in three straight lines intersecting at one point. Good straight line fits for all three lines are obtained by fitting the data to the equation:

$$\text{Log}(y) = aX + b \quad \text{[Equation 3]}$$

The results of such fits are shown in Figure 2A with the dashed blue line representing the cells AGS, U87, PECA4197, BMGI; the solid red line representing the cells PC3, BJ, RT112, PECA4451, HT-29, U1, GT98, Be11, and the dotted green line representing the cells DU145, T98G, A549, SQ20B. Only two cell lines did not fit to any of these lines. These are the MeWo and SCC61 data. One possible explanation is that they could perhaps belong to other lines. Furthermore, the survival data points for T98G were taken from two experiments and there seems to be significant differences between the two.[17,20] One group fitted well with the solid red line while the other group fitted well to the dotted green line.[17,20]

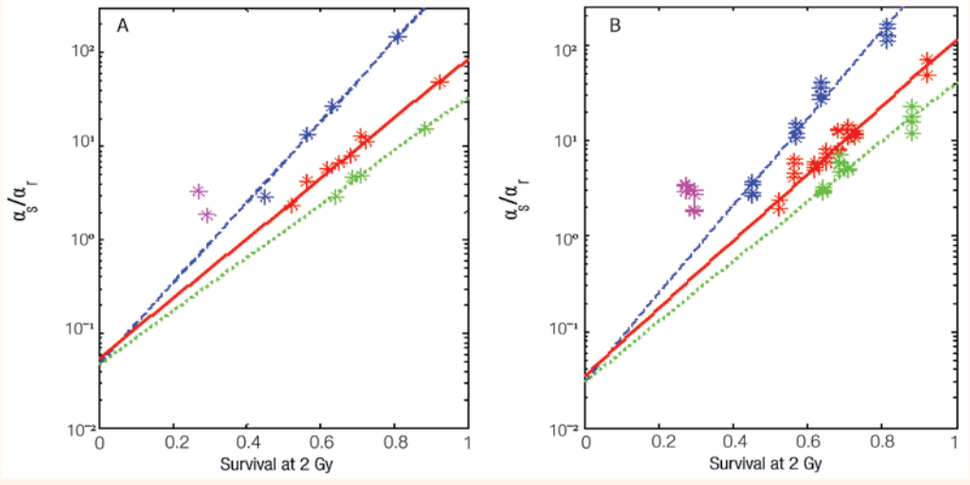

Figure 2 A & B. Fitted lines to Equation 3. **A:** using α_s from best fits to the repairable-conditionally repairable (RCR) model and α_r from best fits to the linear-quadratic (LQ) model, and **B:** using α_s derived from fitting smoothed and non-smoothed data to the RCR model and α_r from fitting smoothed and non-smoothed data to the LQ model.

Table 2: The *a* and *b* parameters obtained from fitting lines 1–3 to the equation ± standard deviation

Data type	Fitting parameters for Line 1		Fitting parameters for Line 2		Fitting parameters for Line 3	
	a	b	a	b	a	b
α_s from best RCR fit/α_r from best LQ fit	4.30 ± 0.85	-1.32 ± 0.53	3.20 ± 0.25	-1.26 ± 0.17	2.85 ± 0.62	-1.33 ± 0.45
α_s from all RCR fit/α_r from all LQ fit	4.60 ± 0.19	-1.52 ± 0.12	3.53 ± 0.21	-1.47 ± 0.14	3.15 ± 0.26	-1.53 ± 0.19
α_s from best IR fit /α_r from best LQ fit	4.76 ± 0.64	-1.55 ± 0.40	4.09 ± 0.39	-1.74 ± 0.26	3.04 ± 0.69	-1.37 ± 0.51
α_s from all IR fit/α_r from all LQ fit	4.99 ± 0.36	-1.77 ± 0.23	4.06 ± 0.31	-1.75 ± 0.20	3.02 ± 0.32	-1.35 ± 0.23
α_s from all data fit/α_r from all LQ fit	4.73 ± 0.23	-1.58 ± 0.15	3.81 ± 0.18	-1.60 ± 0.12	2.97 ± 0.36	-1.35 ± 0.26

RCR = repairable-conditionally repairable; LQ = linear-quadratic; IR = inducible repair.

In order to exclude the possibility that the data points were not biased by the smoothing process, we plotted the combined data values of αs/αr from both the RCR model and the LQ model. In this case, a set of 4 values of α_s/α_r for each SF2 value was obtained. These were α_s smoothed/α_r smoothed, α_s non-smoothed/α_r non-smoothed, α_s smoothed/α_r non-smoothed and α_s non-smoothed/α_r smoothed. Similar results were obtained, as seen in Figure 2B. The procedure was repeated for the case of the IR model (i.e. α_s was taken from the IR model fits and α_r values were taken from the LQ model fits). The results that correspond to Figures 2A and B in the RCR model are shown as Figures 3A and B for the IR model case. The three straight lines obtained were also fitted to Equation 3. The results of fits indicate that the values of the parameters *a* and *b* in the case of the IR model are slightly higher than those in the case of the RCR model.

The final cross-check employed involved plotting all the data points from both models (8 values of αs/αr for each SF2 value). Self-consistent results were obtained as shown in Figure 4. The fitted *a* and *b* parameters obtained by fitting Equation 3 to the lines shown in Figures 2–4 are shown in Table 2, with columns 2 and 3 represent the dashed blue line (Line 1) parameters, columns 4 and 5 represent the solid red line (Line 2) parameters and columns 6 and 7 represent the dotted green line (Line 3) parameters.

Discussion

As seen from Table 2, all fits gave very close results for the *a* and *b* parameters. This was independent of whether the α_s was taken from the IR model fits or the RCR model fits, or when the α_s from the IR and the RCR fits were amalgamated. In all cases, the *a*

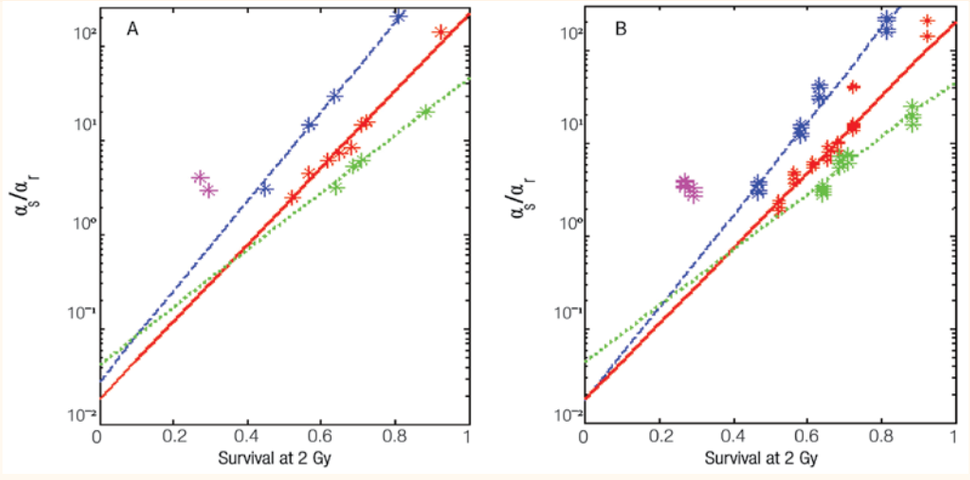

Figure 3 A & B. Fitted lines to Equation 3. **A:** using α_s from best fits to the inducible repair (IR) model and α_r from best fits to the linear-quadratic (LQ) model, and **B:** using α_s derived from fitting smoothed and non-smoothed data to the IR model and α_r from fitting smoothed and non-smoothed data to the LQ model.

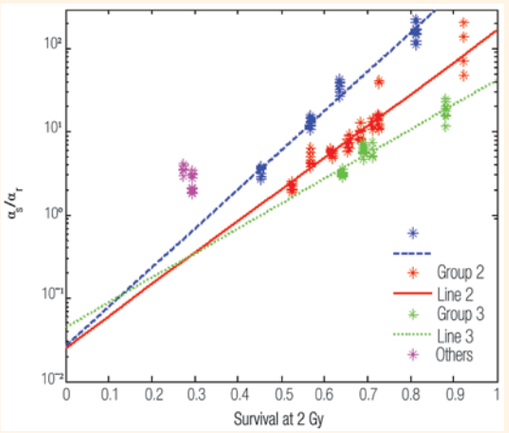

Figure 4: Fitted lines to Equation 3 using α_s from smoothed and non-smoothed fits to the inducible repair (IR) model and the repairable-conditionally repairable (RCR) model and α_r from smoothed and non-smoothed fits to the linear-quadratic (LQ) model.

and *b* values obtained proved to be consistent. The results confirmed the log-linear relation between α_s/α_r and SF2. This represents a diversion from the method suggested by Dasu and Kamp which involved plotting α_s/α_r on a linear scale.[12] In their work, an attempt to find a linear relation resulted in inadequate fits. It may be worth mentioning, however, that their work involved the use of data for different cell lines while only human tumour cell lines were used in the present work. Furthermore, the procedure used by Dasu and Kamp depended on the IR model which fits the HRS/IRR part of the survival curve only but fails to fit the conventional part (>1Gy) in a one-fit process.

The present work involved fitting each part separately, helping to give more precise values for the fit parameters. Also, Joiner *et al.* used published data to find a relation between α_s/α_r and SF2.[1] Their results showed some kind of logarithmic linear relationship but no fitting was provided. This may be due to the interference between the human tumour cell lines and other cell lines which makes the picture less clear.

It may thus be argued that the use of logarithmic procedure can be important in radiotherapy. This is due to the fact that the intrinsic radiosensitivity at clinically relevant doses is directly linked to the cell's ability to mount an adaptive response as a result of exposure to very low doses of radiation. The survival at 2 Gy doses, which is usually used in dose fractionation, is believed to be affected by the HRS/IRR phenomenon. It may cause the tumour to grow again. So, a revision of dose fractionation is required with the need to study each cell line separately.

Conclusion

Precisely fitting parameters that describe the HRS at low doses of radiation α_s and the survival in the shoulder region α_r are obtained by dividing the survival curve data points into two groups. The first group (<1 Gy) fits well to the IR and the RCR models. The second group (>1 Gy plus 0 Gy point) fits well to the LQ model. The α_s/α_r ratio plotted on a logarithmic scale against the survival at 2 Gy as a linear scale displays a series of straight lines. The lines are well-fitted to a logarithmic-linear relation with two parameters *a* and *b* with good quality fits. The relations obtained imply that there is a direct link between the HRS/IRR ratio and the survival at the clinically relevant dose of 2 Gy.

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