Hypersensibilité Cellulaire aux Faibles Doses de Radiation

Phénomène HRS/IRR dans le Domaine des Centigrays

Mécanismes Moléculaires et Modèles Explicatifs

GM

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1 Introduction

1.1 Définition du phénomène HRS/IRR

L'hyper-radiosensibilité aux faibles doses (HRS) décrit un phénomène par lequel les cellules présentent une sensibilité excessive à de petites doses uniques de rayonnement ionisant, typiquement inférieures à 20-50 cGy selon la lignée cellulaire. Ce phénomène n'est pas prédit par l'extrapolation rétrograde de la réponse de survie cellulaire à partir des doses plus élevées utilisant le modèle linéaire-quadratique (LQ) standard.

> ***L'HRS se manifeste par une pente initiale de la courbe de survie (α_s) significativement plus élevée que celle observée à doses plus importantes (α_r), avec un rapport α_s/α_r typiquement compris entre 2 et 5.***

À mesure que la dose augmente au-delà d'environ 20-40 cGy, on observe une augmentation de la radiorésistance (IRR) jusqu'à ce que, au-delà d'environ 1 Gy, la radiorésistance soit maximale et que la survie cellulaire suive la courbe descendante habituelle décrite par le modèle LQ.

1.2 Plages de doses caractéristiques

Phase	Plage de dose	Caractéristique
HRS maximale	5–20 cGy	Hypersensibilité marquée
Transition (Dc)	20–40 cGy	Point d'inflexion
IRR	40–100 cGy	Radiorésistance induite
Comportement LQ	$>$ 100 cGy	Modèle classique

Plages de doses caractéristiques du phénomène HRS/IRR

1.3 Historique des découvertes

Le phénomène a d'abord été observé in vivo par Joiner et Johns en 1988 dans des études sur les dommages rénaux chez la souris. La première démonstration in vitro a été réalisée par Marples et Joiner en 1993 sur les cellules V79 de hamster chinois, où ils ont montré que l'effet par unité de dose augmentait d'un facteur $\sim$2, passant de 0,19 Gy^{-1} à 1 Gy à 0,37 Gy^{-1} à 0,1 Gy.

2 Mécanismes Moléculaires Expliquant l'HRS

2.1 Le modèle centré sur la phase G2

Les données expérimentales démontrent fortement que l'HRS est exclusivement associée à la réponse de survie des cellules en phase G2 du cycle cellulaire. Ce concept "G2-centrique" est apparu lorsque le profil de survie caractéristique de l'HRS n'a pas été détecté dans les populations cellulaires enrichies en phase G1 ou S.

Mécanisme

Observations clés :

- Les cellules T98G et V79 en phase G2 montrent une HRS exagérée
- Les cellules U373 (HRS-négatives en asynchrone) montrent l'HRS uniquement en G2
- L'enrichissement en G2 amplifie la réponse HRS
- L'abrogation du checkpoint G2 augmente la radiosensibilité aux faibles doses

2.2 Le checkpoint G2/M précoce et le seuil d'activation ATM

Deux checkpoints G2/M distincts sont activés après exposition aux rayonnements ionisants, selon le compartiment du cycle cellulaire dans lequel les cellules sont irradiées :

2.2.1 Checkpoint G2 précoce (ATM-dépendant)

- Empêche la progression des cellules irradiées en G2 vers la mitose
- Nécessite l'activité ATM pour les doses $>$ 0,5 Gy
- Possède un **seuil d'activation dose-dépendant** selon la lignée cellulaire
- N'est **pas activé** en dessous d'environ 20-30 cGy dans les lignées HRS-positives

2.2.2 Accumulation G2/M (ATM-indépendante)

— Bloque en G2 les cellules qui étaient en phases plus précoces lors de l'irradiation
— ATM-indépendant mais dose-dépendant
— Implique la voie ATR/Chk1
— Activé dès 0,2 Gy

2.3 Seuil d'activation ATM : le nœud du problème

La protéine ATM (Ataxia Telangiectasia Mutated) est le régulateur principal du checkpoint G2 précoce. Son activation présente un profil dose-réponse caractéristique :

Dose	Réponse ATM
< 10 cGy	Pas d'augmentation mesurable de la phosphorylation ATM-Ser1981 jusqu'à 4h post-irradiation
25 cGy	Augmentation 2-4× de la phosphorylation ATM-Ser1981
> 50 cGy	Activation complète du checkpoint
~ 1 Gy	Saturation de l'activité kinase ATM

Table 2 – *Profil dose-réponse de l'activation ATM*

Les cellules T98G et V79, qui présentent l'HRS, échouent à arrêter l'entrée en mitose des cellules G2 endommagées à des doses inférieures à 30 cGy, comme déterminé par l'évaluation de la phosphorylation de l'histone H3.

2.4 Cascade de signalisation et réparation de l'ADN

2.4.1 Voie de signalisation

1. **Reconnaissance des dommages** : Le complexe MRN (MRE11-RAD50-NBS1) reconnaît les cassures double-brin (DSB)
2. **Activation ATM** : ATM est activée par autophosphorylation sur Ser1981
3. **Phosphorylation de substrats** :
   — H2AX → γH2AX (marqueur des DSB)
   — Chk2 → pChk2 (arrêt du cycle)
   — p53 → activation de la réponse apoptotique
4. **Arrêt du cycle** : Blocage de la transition G2→M via Cdc25C

2.4.2 Réparation des DSB

Les données montrent que la réparation des DSB est moins efficace aux très faibles doses :

— **24h après 25 cGy** : Réduction efficace des foci γH2AX
— **24h après 10 cGy** : Réduction **moins efficace** des foci γH2AX

Ceci suggère que la réparation des DSB est plus efficace pendant la phase IRR que pendant la phase HRS.

2.5 Rôle de l'apoptose

L'HRS est associée à un processus apoptotique dépendant de p53 et de la caspase-3. Les cellules en phase G2 sont particulièrement vulnérables car, en l'absence d'activation du checkpoint précoce, elles progressent vers la mitose sans réparation adéquate, entraînant la mort cellulaire.

2.6 Synthèse du modèle mécanistique actuel

Dose	ATM	Checkpoint G2	Réparation	Survie
$<$ 10-20 cGy	Insuffisante	Non activé	Inefficace	Faible (HRS)
20-50 cGy	Activée	Activé	Efficace	Augmentée (IRR)
$>$ 1 Gy	Maximale	Activé	Efficace	Modèle LQ

Table 3 – *Récapitulatif du mécanisme HRS/IRR*

2.7 Études fondatrices

1. **Joiner MC, Johns H (1988)**.
   Renal damage in the mouse : the response to very small doses per fraction.
   Radiation Research, 114(2) :385-398.
   PMID : 3375433
   https://pubmed.ncbi.nlm.nih.gov/3375433/
   Expériences utilisant des doses de rayons X de 0.2 à 1.6 Gy par fraction et des neutrons de 0.05 à 0.25 Gy par fraction sur les reins de souris.

2.8 Premières études in vitro sur lignées cellulaires (1993–1997)

2. **Marples B, Joiner MC (1993)**.
   The response of Chinese hamster V79 cells to low radiation doses : evidence of enhanced sensitivity of the whole cell population.
   Radiation Research, 133(1) :41-51.
   PMID : 8434112
   https://pubmed.ncbi.nlm.nih.gov/8434112/
   Mesures haute résolution de la survie des cellules V79-379A après doses uniques de rayons X (0.01–10.0 Gy). L'effet par unité de dose a augmenté d'un facteur ∼2, passant de 0.19 Gy^{-1} à 1 Gy à 0.37 Gy^{-1} à 0.1 Gy.
3. **Lambin P, Marples B, Fertil B, Malaise EP, Joiner MC (1993)**.
   Hypersensitivity of a human tumour cell line to very low radiation doses.
   International Journal of Radiation Biology, 63 :639-650.
   PMID : 8099110
   https://pubmed.ncbi.nlm.nih.gov/8099110/
4. **Malaise EP, Lambin P, Joiner MC (1994)**.
   Radiosensitivity of human cell lines to small doses. Are there some clinical implications ?
   Radiation Research, 138(1 Suppl) :S25-27.
   PMID : 8146319
   https://pubmed.ncbi.nlm.nih.gov/8146319/
   Revue utilisant cytométrie de flux et DMIPS montrant l'hypersensibilité à très faibles doses (<0.5 Gy) suivie d'une augmentation de radiorésistance.
5. **Lambin P, Fertil B, Malaise EP, Joiner MC (1994)**.
   Multiphasic Survival Curves for Cells of Human Tumor Cell Lines : Induced Repair or Hypersensitive Subpopulation ?
   Radiation Research, 138(1 Suppl) :S32-S36.
   PMID : 8146321
   https://www.jstor.org/stable/3578756
6. **Wouters BG, Skarsgard LDb(1994)**.
   The response of a human tumor cell line to low radiation doses : Evidence of enhanced sensitivity.
   Radiation Research, 138(1 Suppl) :S76-S80.
   https://pubmed.ncbi.nlm.nih.gov/8146333/
7. **Marples B, Adomat H, Koch CJ, Skov KA (1996)**.
   Response of V79 cells to low doses of X-rays and negative pi-mesons : Clonogenic survival and DNA strand breaks.
   International Journal of Radiation Biology, 70(4) :429-436.
   https://pubmed.ncbi.nlm.nih.gov/8862454/
8. **Wouters BG, Sy AM, Skarsgard LD (1996)**.
   Low-Dose Hypersensitivity and Increased Radioresistance in a Panel of Human Tumor Cell Lines with Different Radiosensitivity.

Radiation Research, 146(4) :399-413.

https://pubmed.ncbi.nlm.nih.gov/8927712/

Étude de 5 lignées tumorales humaines avec sensibilités variables. Les 4 lignées les plus résistantes montrent une hypersensibilité initiale aux faibles doses suivie d'une augmentation de radiorésistance entre 0.3 et 0.7 Gy.

9. **Skarsgard LD, Skwarchuk MW, Wouters BG, Durand RE (1996)**.
Substructure in the radiation survival response at low dose in cells of human tumor cell lines.
Radiation Research, 146(4) :388-398.
https://pubmed.ncbi.nlm.nih.gov/8927711/

10. **Joiner MC, Lambin P, Malaise EP, Robson T, Arrand JE, Skov KA, Marples B (1996)**.
Hypersensitivity to very-low single radiation doses : its relationship to the adaptive response and induced radioresistance.
Mutation Research, 358(2) :171-183.
https://pubmed.ncbi.nlm.nih.gov/8946022/

Revue établissant qu'une petite dose de conditionnement (<30 cGy) peut protéger contre une exposition ultérieure plus importante (réponse adaptative).

11. **Marples B, Lambin P, Skov KA, Joiner MC (1997)**.
Low dose hyper-radiosensitivity and increased radioresistance in mammalian cells.
International Journal of Radiation Biology, 71(6) :721-735.
https://pubmed.ncbi.nlm.nih.gov/9246186/

Revue des travaux du Gray Laboratory (UK) et du BC Cancer Research Centre (Canada) sur l'HRS détectée après doses uniques de rayons X <0.3 Gy et la réponse IRR jusqu'à 1 Gy.

12. **Wouters BG, Skarsgard LD (1997)**.
Low-dose radiation sensitivity and induced radioresistance to cell killing in HT-29 cells is distinct from the 'adaptive response' and cannot be explained by a subpopulation of sensitive cells.
Radiation Research, 148(5) :435-442.
https://pubmed.ncbi.nlm.nih.gov/9355868/

2.9 Etudes sur lignees specifiques (1999–2004)

13. **Short S, Mayes C, Woodcock M, Johns H, Joiner MC (1999)**
Low dose hypersensitivity in the T98G human glioblastoma cell line.
International Journal of Radiation Biology, 75(7) :847-855.
PMID : 10489896
https://pubmed.ncbi.nlm.nih.gov/10489896/
Note : T98G montre une HRS marquee, caracteristique de toute la population cellulaire plutot que d'une sous-population hypersensible.

14. **Vaganay-Juery S et al. (2000)**
Decreased DNA-PK activity in human cancer cells exhibiting hypersensitivity to low-dose irradiation.
British Journal of Cancer, 83(4) :514-518.
PMID : 10945500
https://pubmed.ncbi.nlm.nih.gov/10945500/
Note : Etude de 10 lignees cancereuses humaines montrant une diminution marquee de l'activite DNA-PK dans les 6 lignees presentant HRS apres irradiation a 0.2 Gy.

A Joiner MC, Johns H (1988)

Radiat Res., Vol.114(2), pp.385-98, 1988

Renal damage in the mouse : the response to very small doses per fraction

M C Joiner, H Johns

Experiments were undertaken to study the effect on the mouse kidney of repeated X-ray doses in the range 0.2 to 1.6 Gy per fraction and neutron doses in the range 0.05 to 0.25 Gy per fraction. A top-up design of experiment was used, so that additional graded doses of d(4)-Be neutrons ($\boldsymbol{EN}$ = 2.3 MeV) were given to bring the subthreshold damage produced by these treatments into the measurable range. This approach avoided the necessity to use a large number of fractions to study low doses per fraction. Renal damage was assessed using three methods : 51Cr-EDTA clearance, urine output, and hematocrit at 16-50 weeks postirradiation. The dose-response curves obtained were resolved best at 29 weeks. However, the results were also examined by fitting second-order polynomials to the data for response versus time postirradiation and using interpolated values from these functions at 29 weeks to construct dose-response curves. This method reduced slightly the variation in the dose-response data, but the interrelationship between the dose-response curves remained the same. The data were used to test the linear-quadratic (LQ) description of the underlying X-ray dose-fractionation relationship. The model fits well down to X-ray doses per fraction of approximately 1 Gy, but lower X-ray doses were more effective per gray than predicted by LQ, as seen previously in skin [M. C. Joiner et al., Int. J. Radiat. Biol. 49, 565-580 (1986)]. This increased X-ray effectiveness and deviation from LQ are reflected directly in a decrease in the RBE of d(4)-Be neutrons relative to X-rays at low doses, since the underlying response to these neutrons is linear in this low-dose region. The RBE decreases from 9.9 to 4.7 as the X-ray dose per fraction is reduced below 0.8 Gy to 0.2 Gy, reflecting an increase in X-ray effectiveness by a factor of 2.1. A model is discussed which attempts to explain this behavior at low doses per fraction.

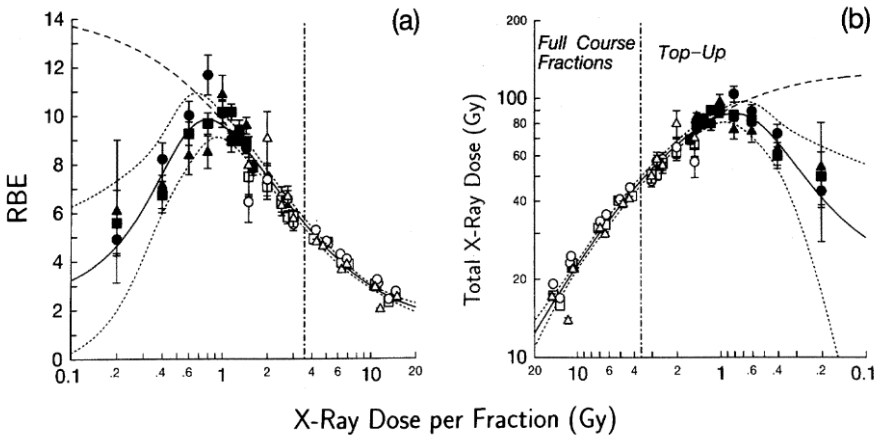

FIG. 7. All available data from comparisons between 240 kVp X rays and d(4)-Be neutrons in the mouse kidney, plotted as (a) RBE between X rays and neutrons or (b) isoeffective X-ray doses to give 3% residual activity, 40% hematocrit, or 15 urination events per day, at 29 weeks postirradiation. Closed symbols, present data. Open symbols, previous data summarized by Joiner and Johns (*21*). Squares, EDTA clearance. Circles, hematocrit. Triangles, urination frequency. The solid lines are the fit to all the data using a model incorporating increasing X-ray sensitivity at very low X-ray doses per fraction, with the dotted lines showing the 95% confidence limits on the mean (expected) values from this fit. Above 1 Gy per fraction, the model rapidly approaches a simple LQ fit, as shown by the dashed line.

B Marples B, Joiner MC (1993)

Radiation Research, Vol.133(1), pp.41-51, 1993

The response of Chinese hamster V79 cells to low radiation doses : evidence of enhanced sensitivity of the whole cell population

B Marples, M C Joiner

High-resolution measurements of the survival of asynchronous Chinese hamster V79-379A cells in vitro after single doses of X rays (0.01-10.0 Gy) and neutrons (0.02-3.0 Gy) were made using a computerized microscope for locating and identifying cells (Palcic and Jaggi, Int. J. Radiat. Biol. 50, 345-352, 1986). The X-ray response from 1 to 10 Gy showed a good fit to a linear-quadratic (LQ) dose-survival model, but with X-ray doses below 0.6 Gy, an increased X-ray effectiveness was observed, with cell survival below the prediction made from the data above 1 Gy using the LQ model. The effect per unit dose (-log(e)SF/dose) increased by a factor of approximately 2, from 0.19 Gy-1 at a dose of 1 Gy to 0.37 Gy-1 at a dose of 0.1 Gy. This phenomenon was not seen with neutrons, and cell survival decreased exponentially over the whole neutron dose range studied. Further data suggest that this phenomenon is unlikely to be due to a subpopulation of X-ray-sensitive cells determined either genetically or phenotypically by distribution of the population within the cell cycle. The existence of low-dose sensitivity also appeared to be independent of dose rate in the range 0.016-1.7 Gy min-1. A possible explanation of these results is that the phenomenon reflects "induced repair" or a stress response : low doses in vitro (or low doses per fraction in vivo) are more effective per gray than higher doses because only at the higher doses is there sufficient damage to trigger repair systems or other radioprotective mechanisms.

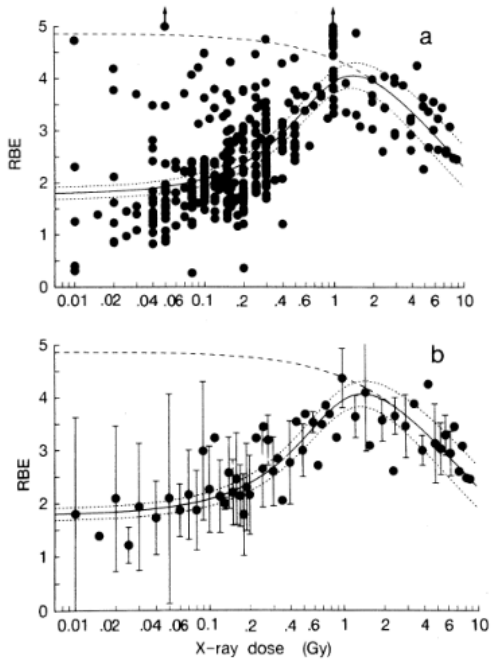

FIG. 4. Relative biological effectiveness (RBE) between 250-kVp X rays and d(4)-Be neutrons plotted against X-ray dose. Smaller RBE means greater X-ray effect per unit dose. The RBE value was calculated for each individual measurement of X-ray survival, relative to the fit to the neutron data obtained within the same experiment (see text). Panel (a) shows all the individual measurements and panel (b) shows the data as mean values ± SD. Solid lines show the fit of an "induced repair" model to the data (see text) with 95% confidence limits on the mean (expected) prediction shown as dotted lines. The dashed lines show how a linear-quadratic model of X-ray response fits the data at doses ≥ 1 Gy, but significantly underestimates the effect of X rays at lower doses.

C P Lambin, B Marples, B Fertil, E P Malaise, M C Joiner (1993)

Int J Radiat Biol.,Vol.63(5), pp.639-50, 1993
Hypersensitivity of a human tumour cell line to very low radiation doses
P Lambin, B Marples, B Fertil, E P Malaise, M C Joiner

Survival of HT29 cells was measured after irradiation with single doses of X-rays (0.05-5 Gy) and neutrons (0.025-1.5 Gy), using a Dynamic Microscopic Imaging Processing Scanner (DMIPS) with which individual cells can be accurately located in tissue culture flasks, their positions recorded, and after an appropriate incubation time the recorded positions revisited to allow the scoring of survivors. The response over the X-ray dose range 2-5 Gy showed a good fit to a Linear-Quadratic (LQ) model. For X-ray doses below 1 Gy, an increased X-ray effectiveness was observed with cell survival below the high-dose LQ prediction. The value of –dose/loge (SF) for each experimental data point, plotted against dose, demonstrated clearly how X-rays are maximally effective at doses approaching zero, becoming less effective as the dose increases and with minimal effectiveness at about 0.6 Gy then becoming more effective again as the dose increases above 1.5 Gy. This phenomenon was not seen with neutrons. Neutron RBE was calculated for each X-ray data point by taking each X-ray survival value and comparing it with the common LQ fit to all the neutron data. Over the X-ray dose range 0.05-0.2 Gy, the RBE is close to 1 indicating that these very low doses of X-rays are of similar effectiveness to neutrons in killing cells. The increase in RBE with increasing dose over the range 0.05-1 Gy, and the slight decrease in RBE above 1 Gy, reflect primarily the changes in X-ray sensitivity over the whole dose range of 0.05-5 Gy. Several arguments suggest that this phenomenon could reflect an induced radioresistance so that in this system low single doses of X-rays are more effective per Gy than higher doses in reducing cell survival because only at higher doses, above a threshold, is there sufficient damage to trigger radioprotective mechanisms.

D E P Malaise, P Lambin, M C Joiner (1994)

Radiat Res., Vol.138(1 Suppl),pp.S25-7, 1994
Radiosensitivity of human cell lines to small doses. Are there some clinical implications ?
E P Malaise, P Lambin, M C Joiner

The concept of intrinsic radiosensitivity is now strongly associated with the linear-quadratic (LQ) model which is currently the best and the most reliable method to fit the first three decades of a survival curve for both human fibroblast and human tumor cell lines. This approach has led to the major conclusions that it is the initial part, and not the distal part, of the survival curve which truly characterizes intrinsic cellular radiosensitivity and there is a correlation between the parameters describing mainly the initial part of the survival curve (α, $SF2$, D) and the clinical radioresponsiveness. More accurate analysis with flow cytometry or a dynamic microscopic image processing scanner ($DMIPS$) has allowed further study of the survival curve which has shown two sorts of substructure. On one hand, the overall survival curve of exponentially growing cells is described by two or more sets of alpha, beta parameters (heterogeneity in radiosensitivity due to the cell cycle). On the other hand, hypersensitivity at very low doses (< 0.5 Gy) followed by an increase of the radioresistance of the whole population at higher doses has also been observed. This phenomenon is not described by the conventional LQ model and has been interpreted as an induced radioresistance which seems to be negatively correlated with intrinsic radiosensitivity. In clinical radiotherapy, there are two sorts of response of normal tissues : (1) the early and late damage and (2) the carcinogenesis. Concerning the first point, the clinically detectable radiation damage appears at doses usually around 20 Gy (in 2-Gy fractions) with the exception of the hemopoietic and the lymphatic tissues. Therefore, the small doses delivered at the edges or in the penumbrae of treatment fields in routine radiotherapy cannot create detectable damage, despite a potentially much higher effect per unit dose, because the total doses are still very small. However, it may be important to bear in mind the possible extra effect of low doses outside the target volume if regions in the vicinity are subsequently retreated. Concerning clinical radiation-induced carcinogenesis, three studies described a higher relative risk associated with small doses per fraction or very low dose rate. The results and the interpretation of these studies are discussed.

E P. Lambin, B. Fertil, E. P. Malaise, M. C. Joiner (1994)

Radiation Research, Vol.138(1), 1994

Multiphasic Survival Curves for Cells of Human Tumor Cell Lines : Induced Repair or Hypersensitive Subpopulation ?

P. Lambin, B. Fertil, E. P. Malaise, M. C. Joiner

Survival of the cells of three human tumor cell lines of differing radiosensitivity was measured after irradiation with single doses of X rays (0.05-5 Gy). At doses below 1 Gy, cells were more radiosensitive than predicted by back-extrapolating the high-dose response. This difference was more marked for cells of the radioresistant cell lines than the radiosensitive cell line so that the "true" initial slopes of the survival curves, at very low doses, were similar for the cells of the three cell lines. This phenomenon could reflect an induced radioresistance so that low doses of X rays are more effective per gray than higher doses, because only at higher doses is there sufficient damage to trigger repair systems or other radioprotective mechanisms which can then act during the time course for repair of DNA injury

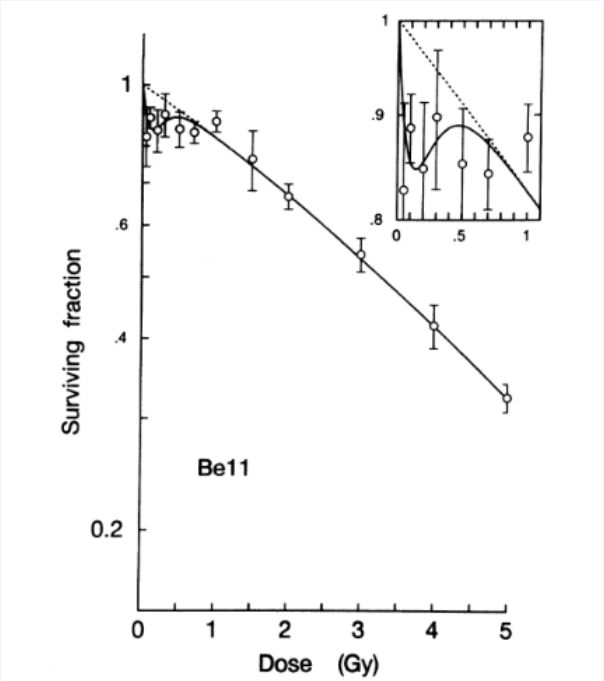

FIG. 1. Survival of radioresistant Be11 cells irradiated with 240 kVp X rays. Data points show the mean ± SEM of four experiments with multiple repeats at some doses (generally between five and seven determinations of survival per dose). The dotted line shows the fit of the linear-quadratic model to the X-ray data at ≥2 Gy. The solid line shows the fit of the induced repair model to all the X-ray data. At X-ray doses <1 Gy, the LQ model substantially underpredicts the effect of X rays, which is better fitted by the induced repair model. The inset shows the region of the survival curve between 0 and 1 Gy magnified.

F B G Wouters , L D Skarsgard (1994)

Radiat Res., Vol.138(1 Suppl), pp.S76-80, 1994
The response of a human tumor cell line to low radiation doses : evidence of enhanced sensitivity
B G Wouters , L D Skarsgard

The survival of asynchronous, exponentially growing DU-145 human tumor cells was measured after single doses of X rays in the dose range of 0.05-4 Gy using the cell sorting assay. When the response was modeled with the linear-quadratic (LQ) equation, a good fit to the data was observed for dose levels above 1 Gy ; however, a region of enhanced sensitivity was observed at doses less than this. One possible explanation of this low-dose substructure is that a small, sensitive subpopulation of cells is selectively killed at low doses. Modeling of the radiation response with a two-population LQ model suggests that for these data this explanation is unlikely. Another possibility is that the whole cell population is initially hypersensitive, becoming radioresistant as damage is sustained by the cell. Conceivably this radioprotective mechanism could act in one of two ways. The cell could move from a radiation-sensitive to a radiation-resistant state by a continuous function of dose, or alternatively, only after a sufficient accumulation of damage, i.e. a "triggering dose." Both of these possibilities have been explored in the results of fitting two "induced resistance" models.

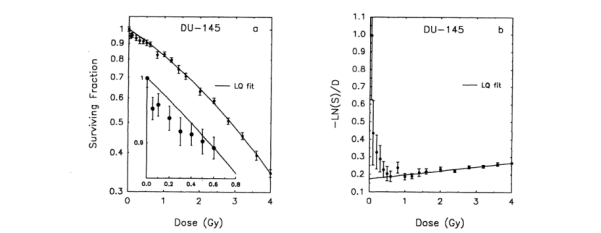

FIG. 1. Survival data for DU-145 cells irradiated at 37°C in suspension under aerobic conditions. Data are the average of eight experiments. Error bars are the standard error in the mean. Data are plotted in the form a) surviving fraction vs dose, and b) $-(\ln S)/D$ vs D. The fitted lines represent the best fit of the data to the LQ equation, $S = \exp(-\alpha D - \beta D^2)$, over the dose range (1 to 4 Gy).

G Marples B, Adomat H, Koch CJ, Skov KA (1996)

Int J Radiat Biol., Vol.70(4),pp. 429-36, 1996
Response of V79 cells to low doses of X-rays and negative pi-mesons : clonogenic survival and DNA strand breaks
B Marples, H Adomat, C J Koch, K A Skov

Mammalian cells are hypersensitive to very low doses of X-rays (< 0.2 Gy), a response which is followed by increased radioresistance up to 1 Gy. Increased radioresistance is postulated to be a response to DNA damage, possibly single-strand breaks, and it appears to be a characteristic of low linear energy transfer (LET) radiation. Here we demonstrate a correspondence between the extent of the increased radioresistance and linear energy transfer of 250 kVp X-rays and plateau and Bragg peak negative pi-mesons. The results support our hypothesis since the size of the increased radioresistant response appears to correspond to the number of radiation induced single-strand breaks. Furthermore, since survival prior to the increased radioresistant response (< 0.2 Gy) was LET-independent, these data support the notion that the increased radioresistant response may dictate the overall survival response to higher doses. However, while these data provide further circumstantial evidence for the involvement of DNA strand breaks in the triggering of increased radioresistance, more direct conclusions cannot be made. The data are not accurate enough to detect structure in the single-strand break profiles, the production of single-strand breaks being apparently linear with dose

H B G Wouters, A M Sy, L D Skarsgard (1996)

Radiat Res., Vol.146(4), pp.399-413, 1996

Low-dose hypersensitivity and increased radioresistance in a panel of human tumor cell lines with different radiosensitivity

B G Wouters, A M Sy, L D Skarsgard

It is well known that cells of human tumor cell lines display a wide range of sensitivity to radiation, at least a part of which can be attributed to different capacities to process and repair radiation damage correctly. We have examined the response to very low-dose radiation of cells of five human tumor cell lines that display varying sensitivity to radiation, using an improved assay for measurement of radiation survival. This assay improves on the precision of conventional techniques by accurately determining the numbers of cells at risk, and has allowed us to measure radiation survival to doses as low as 0.05 Gy. Because of the statistical limitations in measuring radiation survival at very low doses, extensive averaging of data was used to determine the survival response accurately. Our results show that the four most resistant cell lines exhibit a region of initial low-dose hypersensitivity. This hypersensitivity is followed by an increase in radioresistance over the dose range 0.3 to 0.7 Gy, beyond which the response is typical of that seen in most survival curves. Mathematical modeling of the responses suggests that this phenomenon is not due to a small subpopulation of sensitive cells (e.g. mitotic), but rather is a reflection of the induction of resistance in the whole cell population, or at least a significant proportion of the whole cell population. These results suggest that a dose-dependent alteration in the processing of DNA damage over the initial low-dose region of cell survival may contribute to radioresistance in some cell lines.

I L D Skarsgard, M W Skwarchuk, B G Wouters, R E Durand (1996)

Radiat Res., Vol.146(4), pp.388-98, 1996 1996

Substructure in the radiation survival response at low dose in cells of human tumor cell lines

L D Skarsgard, M W Skwarchuk, B G Wouters, R E Durand

In earlier studies using asynchronously growing Chinese hamster cells, we observed substructure in the survival response at low doses. The substructure appeared to result from subpopulations of cells having different, cell cycle phase-dependent radiosensitivity. We have now applied the same flow cytometry and cell sorting technique to accurately measure the responses of cells of eight different asynchronously growing human tumor cell lines, representing a wide range in radiosensitivity. When the data were fitted with a linear-quadratic (LQ) function, most of these lines showed substructure similar to that observed in Chinese hamster cells, with the result that values of alpha and beta were dependent on the dose range used for fitting. Values of alpha describing the low-dose response were typically smaller (by as much as 2.2 times) than the alpha describing the high-dose response, while values of beta were larger at low doses. Values of alpha/beta from our measurements are in reasonable agreement with other values published recently if we fit the data for the high-dose range (excluding, for example, 0-4 Gy), which corresponds to a conventional survival response measurement. However, the values of alpha/beta describing the low-dose range were, on average, 2.8-fold smaller. The results show that the usual laboratory measurement of cell survival over 2 or 3 logs of cell killing, if fitted with a single LQ function, will yield alpha and beta values which may give a rather poor description of cell inactivation at low dose in asynchronous cells, no matter how carefully those measurements are done, unless the low-dose range is fitted separately. The contribution of killing represented by the beta coefficient at low doses was found to be surprisingly large, accounting for 40-70% of cell inactivation at 2 Gy in these cell lines. A two-population LQ model provides excellent fits to the data for most of the cell lines though, as one might expect with a five-parameter model, the best-fitting value of the various parameters is far from unique, and the values are probably not reliable indicators of the size and radiosensitivity of the different cell subpopulations. At very low dose, below 0.5-1 Gy, another order of substructure is observed : the hypersensitive response ; this is described in the accompanying paper (Wouters et al., Radiat. Res. 146, 399-413, 1996).

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Mutat Res . 1996 Nov 4 ;358(**??**) :171-83. Hypersensitivity to very-low single radiation doses : its relationship to the adaptive response and induced radioresistance M C Joiner , P Lambin, E P Malaise, T Robson, J E Arrand, K A Skov, B Marples

There is now little doubt of the existence of radioprotective mechanisms, or stress responses, that are upregulated in response to exposure to small doses of ionizing radiation and other DNA-damaging agents. Phenomenologically, there are two ways in which these induced mechanisms operate. First, a small conditioning dose (generally below 30 cGy) may protect against a subsequent, separate, exposure to radiation that may be substantially larger than the initial dose. This has been termed the adaptive response. Second, the response to single doses may itself be dose-dependent so that small acute radiation exposures, or exposures at very low dose rates, are more effective per unit dose than larger exposures above the threshold where the induced radioprotection is triggered. This combination has been termed low-dose hypersensitivity (HRS) and induced radioresistance (IRR) as the dose increases. Both the adaptive response and HRS/IRR have been well documented in studies with yeast, bacteria, protozoa, algae, higher plant cells, insect cells, mammalian and human cells in vitro, and in studies on animal models in vivo. There is indirect evidence that the HRS/IRR phenomenon in response to single doses is a manifestation of the same underlying mechanism that determines the adaptive response in the two-dose case and that it can be triggered by high and low LET radiations as well as a variety of other stress-inducing agents such as hydrogen peroxide and chemotherapeutic agents although exact homology remains to be tested. Little is currently known about the precise nature of this underlying mechanism, but there is evidence that it operates by increasing the amount and rate of DNA repair, rather than by indirect mechanisms such as modulation of cell-cycle progression or apoptosis. Changed expression of some genes, only in response to low and not high doses, may occur within a few hours of irradiation and this would be rapid enough to explain the phenomenon of induced radioresistance although its specific molecular components have yet to be identified.