A Cell Killing Model That Includes the Effects of Chromatin Structure.

II. Proliferating Cells.

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Abstract

A molecular-level radiobiological model has been developed and used to investigate the biological basis for cell cycle effects in Chinese hamster V79 cells. The proposed model accounts for the heterogeneous formation and repair of DNA damage in heterochromatin, two types of euchromatin, and just-replicated nascent euchromatin. The proposed model also accounts for damage-induced cell cycle blocking, temporal changes in the structure of a cell's chromatin, and desynchronization effects in groups of proliferating cells.

Model sensitivity studies and comparisons of measured and calculated cell survival probabilities indicate the modeling at a molecular level of radiation-induced cell-killing effects in proliferating V79 cells has been successful. Model results suggest that cell cycle changes in chromatin structure produce cyclic changes in the initial yield of DNA damage Gy^{-1} $cell^{-1}$. These cyclic changes in the structure of the chromatin also produce cyclic changes in the rates of DNA damage repair and in the rate the initial DNA damage is converted into lethal types of DNA damage. It is concluded that these phenomena are responsible for observed cell cycle effects. Finally, calculations illustrating the model's use to optimize dose-fractionation patterns in radiotherapy treatment protocols are presented and discussed.

Conclusions

- Cell cycle effects in proliferating Chinese hamster V79 cells can be plausibly explained in terms of cyclic changes in chromatin structure. Changes in chromatin structure produce cyclic changes in the initial yield of DNA damage, the rates of lesion repair, and the rate the initial DNA damage is converted into lethal types of damage.
- S phase V79 cells are more resistant to the harmful effects of ionizing radiation because these cells are better able to repair DNA damage than cells in other phases. It is unlikely that S phase cells are resistant to the effects of ionizing radiation because of a decrease in the initial yield of DNA damage.
- It was found that the best agreement between measured and calculated survival probabilities was obtained when binary misrepair interaction probabilities are set larger in condensed types of chromatin than in unfolded euchromatin. This finding is attributed to proximity effects associated with the formation of groups of spatially correlated double strand breaks.
- The V79 cells used by Sinclair (1969) may not have had a functional G2 phase cell cycle block.
- The mechanistic radiobiological model presented here is a useful tool for the interpretation of radiobiological experiments. Further, this tool could be used to help design optimized radiotherapy treatment protocols tailored to the growth characteristics of specific tumors.

Lesion Balance Equations

For the *g*th cell generation, $t_{g-1} < t < t_g$, and $k = u$ (unreplicated) and r (replicated), n = 1 (*het*), 2 (*tie*), 3 (*tae*), 4 (*nas*)

$$\frac{d\overline{L}_{dsb}^{k,g}(n,t)}{dt} = 2\dot{D}(t)Y_n^k(t)\Sigma_{dsb}(n) - l_{dsb}^k(n)\overline{L}_{dsb}^{k,g}(n,t)$$

$$-\overline{L}_{dsb}^{k,g}(n,t)\left\{e_{dsb\to f}(n,t) + \sum_k \sum_m h_{dsb\to f}(n;m)\overline{L}_{dsb}^{k,g}(m,t)\right\}$$

$$+\sum_{m\neq n}\left[\Gamma^k(m\to n,t)\overline{L}_{dsb}^{k,g}(m,t) - \Gamma^k(n\to m,t)\overline{L}_{dsb}^{k,g}(n,t)\right]$$

$$\frac{d\overline{L}_f^{k,g}(t)}{dt} = \sum_n \overline{L}_{dsb}^{k,g}(n,t)\left\{e_{dsb\to f}(n,t) + \sum_k \sum_m h_{dsb\to f}(n;m)\overline{L}_{dsb}^{k,g}(m,t)\right\}$$

Boundary Conditions

Prior to irradiation, cells are undamaged so that

$$\overline{L}_{dsb}^{k,1}(n,t_0) = \overline{L}_f^{k,1}(t_0) = 0.$$

At the completion of the *g*th mitosis, half the parental DNA is transmitted to each progeny cell and

$$\overline{L}_{dsb}^{u,g+1}(n,t_g^+) = \frac{1}{2}\overline{L}_{dsb}^{r,g}(n,t_g^-)$$

$$\overline{L}_{dsb}^{r,g+1}(t_g^+) = \overline{L}_f^{k,g+1}(t_g^+) = 0$$

A long time after the irradiation ends,

$$\lim_{t\to\infty} \overline{L}_{dsb}^{k,g}(n,t) = 0 \quad \text{and} \quad \lim_{t\to\infty} \overline{L}_f^{k,g}(t) = 0.$$

Calculation of Survival Probabilities

For $t > t_{g-1,}$ the survival probability for the ith group of synchronously proliferating cells of initial age t_0 is

$$S_i(t_0,t) = e^{-\left[\bar{L}_f^{u,g}(t)+\bar{L}_f^{r,g}(t)\right]} \times \left\{1+\frac{1}{2}\sum_{k=1}^{\infty}\left(k!2^k\right)^{-1}\left[\bar{L}_f^{r,g}(t)\right]^k\right\} S_i(t_0,t_{g-1}).$$

The survival probability for a group of cells with an arbitrary initial age distribution $f(t_0)$ is

$$\bar{S}(t) = \int_0^1 dt_0 \;\; f(t_0)\bar{S}(t_0,t)$$

where

$$\bar{S}(t_0,t) = \left\{\sum_{i=1}^{N} 2^{g_i(t_0,t)}\right\}^{-1} \times \sum_{i=1}^{N} 2^{g_i(t_0,t)} S_i(t_0,t).$$

Cell Aging Model

The equation governing the rate of cell aging is

$$\frac{dt}{dt} = w(t) \longrightarrow t(t) = t_0 + \int_{t_0}^{t} dt'\, w(t')$$

The cell aging function $w(t)$ is sampled from a probability density function at intervals of Δt, and Monte Carlo methods are used to evaluate $t(t)$.

$$t(t) = t_0 + \sum_{l=0}^{n-1} w_l \int_{t_l}^{t_l+\Delta t} dt'\, q_1(t)^{\bar{L}_{dsb}(t')} + w_n \int_{t_n}^{t} dt'\, q_1(t)^{\bar{L}_{dsb}(t')}$$

"uniform pdf"

$$p(w) = \begin{cases} \dfrac{1}{2\bar{w}}, & 0 \le w \le 2\bar{w} \\ 0, & \text{otherwise} \end{cases}$$

"binary pdf"

$$p(w) = \left(1 - \frac{1}{m}\right) d(w) + \frac{1}{m}\, d(w - m\bar{w})$$