Expansion of Whack-A-Mole Model to Add Canceration Risk

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On the basis of Whack-A-Model, I expand the model to add canceration risk. The model can explain time-lag effect and threshould of canceration.

Manabe *et al*. proposed the Whack-A-Mole model for estimating biological effects caused by artificial radiation exposure[1-4]. They took into account of the dose-rate effect on the risk estimation of low-dose radiation. I tried to expand their model for including canceration.

$$N \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} I \xrightarrow{k_2} G \quad \text{(Scheme I)}$$

where N and I are normal and mutated cells, respectively, and G is a cell irreversibly induced from I. In other words, I is a cell capable of changing to N reversibly, whereas G cannot go back to I, as canceration trigger is initiated. k_1, k_{-1} and k_2 are corresponding rate defined in the Scheme I. Then,

$$\frac{d[N]}{dt} = k_{-1}[I] - k_1[N] \qquad (1)$$

$$\frac{d[G]}{dt} = k_2[I] \qquad (2)$$

$$\frac{d[I]}{dt} = k_1[N] - (k_{-1} + k_2)[I] \qquad (3)$$

$$[N] + [I] + [G] = c_0 \qquad (4)$$

where total numbers of cells are assumed to be constant and written as c_0.

Assuming $[G] \ll 1$,

$$\frac{d[I]}{dt} = k_1 c_0 - (k_1 + k_{-1} + k_2)[I] \qquad (5)$$

Let's define $\xi = k_1 c_0 - (k_1 + k_{-1} + k_2)[I]$

$$\frac{d\xi}{dt} = -(k_1 + k_{-1} + k_2)\frac{[d[I]]}{dt}$$

$$= -(k_1 + k_{-1} + k_2)\xi \qquad (6)$$

Then $\xi = Ae^{-k_{app}t}$, where k_{app} is defined as $k_1 + k_{-1} + k_2$ and A is a constant.

$$[I] = \frac{k_1}{k_{app}} c_0 - \frac{A}{k_{app}} e^{-k_{app} t} \qquad (7)$$

As $[I]_0 = 0$ at $t = 0$,

$$[I] = \frac{k_1 c_0}{k_{app}}(1 - e^{-k_{app} t}) \qquad (8)$$

From eqs. (2) and (8)

$$[G] = \frac{k_1 k_2 c_0}{k_{app}}\left(t - \frac{1}{k_{app}} e^{-k_{app} t}\right) + B \qquad (9)$$

where B is another constant.

Assuming $[G]_0$=0 at $t = 0$, $B = -\frac{k_1 k_2 c_0}{{k_{app}}^2}$

and then

$$[G] = \frac{k_1 k_2 c_0}{k_{app}} t - \frac{k_1 k_2 c_0}{{k_{app}}^2}\left(1 - e^{-k_{app} t}\right) \quad (10)$$

or $$\frac{[G]}{c_0} = \frac{k_1 k_2}{k_{app}} t - \frac{k_1 k_2}{{k_{app}}^2}\left(1 - e^{-k_{app} t}\right) \quad (11)$$

At $t \ll 1$,

$\frac{[G]}{c_0}$ can be assumed as $\frac{[G]}{c_0} \cong 0$

and then $\frac{[G]}{c_0}$ increases with time

according to the equation

$$\frac{[G]}{c_0} \cong \frac{k_1 k_2}{k_{app}} t - \frac{k_1 k_2}{{k_{app}}^2} = \frac{k_1 k_2}{k_{app}}(t - \tau)$$

where τ is defined as $\tau = \frac{1}{k_{app}}$ (12)

As k_{app} is defined as $k_1 + k_{-1} + k_2$, τ is determined by one of the fastest process of the reaction (the largest value among k_1, k_{-1} and k_2).

At late stage, $\frac{[G]}{c_0}$ increases linearly with

the slope of $\frac{k_1 k_2}{k_{app}}$.

Comparison with Manabe model

Manabe *et al.* developed WAM model by defining N_n and N_m as the number of normal and mutated cells, respectively, and they are described by the differential equations

$$\frac{dN_n}{dt} = R_{nn}N_n + R_{nm}N_m \quad (13)$$

$$\frac{dN_m}{dt} = R_{mn}N_n + R_{mm}N_m \quad (14)$$

where the matrix R represents reaction rate; R_{nn} corresponds to the proliferation or cell death of normal cells, R_{nm} denotes the rate of repair from mutated cells to normal ones, R_{mn} indicates the mutation of normal cells, and R_{mm} corresponds to the proliferation or cell death of mutated cells. They assign R_{nm} = 0 due to the definition of mutation.

Roughly speaking, N_n and N_m correspond to N and I in Scheme I, respectively. However, there is a difference; Damaged DNA s are repaired by ligation, which should be included in the Scheme. Manabe *et al*. assigned this repair to the change from mutated cell to another mutated cell. Thus, k_{-1} in Scheme I should be corresponding to R_{mm} and not to R_{nm} (=0). Manabe model is different from the Scheme I at one more point; I assume total cell number is constant (=c_0) in the derivation above, which corresponds to R_{nn}=0. This is not essential difference. However, to be simple, this assumption is employed.

Thus, k_1 and k_{-1} correspond to R_{mn} and $-R_{mm}$, respectively. Manabe *et al.* have done analyses of stimulus-response procedure with $R_{mn} = a_0 + a_1[S]$ and $R_{mm} = -(b_0 + b_1[S])$ where a_0, a_1, b_0 and b_1 are parameters representing the charasteristics of species and $[S]$ is the dose rate. Though there are some differences, it is agreeable that $k_1 = a_0 + a_1[S]$ and $k_{-1} = b_0 + b_1[S]$.

The slope S_L is rewritten as $\frac{k_2}{1+\frac{k_{-1}+k_2}{k_1}}$, which approaches to $\frac{k_2}{1+\frac{b_1[S]+k_2}{a_1[S]}}$ at high $[S]$. If k_2 does not depend on $[S]$, the slope becomes constant at high $[S]$. This is in apparent contradiction with experimental observation; the slope becomes steeper with the increase of [S].

Then, we assumes $k_2 = d_0+d_1[S]$ in the simplest manner. Then,

$$\tau = {}^{1}/_{\{a_0 + b_0 + d_0 + (a_1 + b_1 + d_1)[S]\}} \quad (15)$$

Eq. (12) shows the lag becomes shorter with the increase of $[S]$.

Manabe *et al.* estimated four parameters according to the experimental data reported by Russel and Kelly[5], and obtained $a_0 = 3.2 \times 10^{-8}\left({}^{1}/_{\mathrm{hr}}\right)$, $a_1 = 30 \times 10^{-5}\left({}^{1}/_{\mathrm{Gy}}\right)$, $b_0 = 2.9 \times 10^{-3}\left({}^{1}/_{\mathrm{hr}}\right)$ and $b_1 = 1.4 \times 10^{-8}\left({}^{1}/_{\mathrm{Gy}}\right)$ [6]. Using these values,

$\tau \cong 300$ hr $= 13$ days at $[S]$, d_0 and $d_1 = 0$. As the averaged life of mice and human being are c.a. 2 years and 80 years, τ seems to be 520 days in human being.

We have no data for estimating d_0 or d_1 in case of mice. Instead, I use 0 for d_0 and 5.5*10^{-5} (1/year) from human canceration risk with 1 mGy exposure[7]. The slope S_L is then 5.5*10^{-5}*10^{3}/(365*24)= 6.3*10^{-6}Gy^{-1}hr^{-1}. d_1 is calculated according to the following equation,

$$S_L(a_1 + b_1 + d_1) = a_1 d_1$$

$$\therefore d_1 = \frac{(a_1 + b_1)S_L}{a_1 - S_L} = 7.94 \times 10^{-6}\mathrm{Gy}^{-1}\mathrm{hr}^{-1}$$

With these values, τ is recalculated as 14.4 days at [S] = 0. $[G]/c_0$, calculated from the values above, is shown in Fig.1. The figure clearly shows the lag phase.

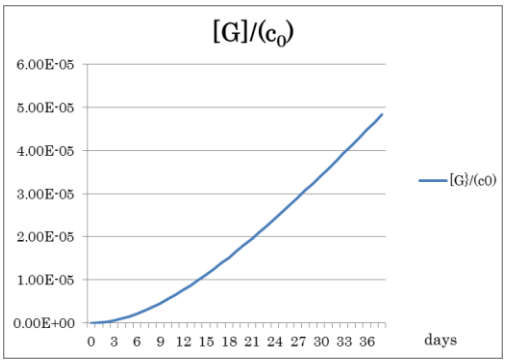

Figure 1. $[G]/c_0$ vs. t. d_0 and d_1 are assumed to be 0 and 7.93*10^{-6} Gy^{-1}, respectively, and $[S]$ =1 Gy/hr.

Slope – dose effect

The slope $\frac{[G]}{c_0} = \frac{k_1 k_2}{k_{app}} \simeq \frac{k_1 k_2}{k_1+k_{-1}+k_2} =$

$$\frac{k_2}{1+\frac{k_{-1}+k_2}{k_1}} = \frac{d_0+d_1[S]}{1+\frac{b_0+d_0+(b_1+d_1)[S]}{a_0+a_1[S]}} \quad (16)$$

Results calculated with these values are shown in Fig. 2.

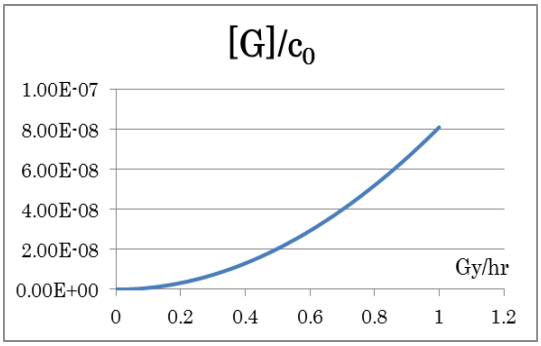

Figure 2. $[G]/c_0$ vs. $[S]$.

The graph shows clearly lag phase against $[S]$, and results don't agree LNT hypothesis[7].

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