CHAPTER TWO
MECHANISMS OF RADIATION EFFECTS

2.0 INTRODUCTION

Cell survival curves describe the relationship between the fractional survival, S, of a population of radiated cells and the dose of the radiation in grays (Gy) to which the cells have been exposed. Survival curves for mammalian cells are usually presented in the form shown in Figure 2.0, with dose plotted on a linear scale and surviving fraction on a logarithmic scale[3,15].

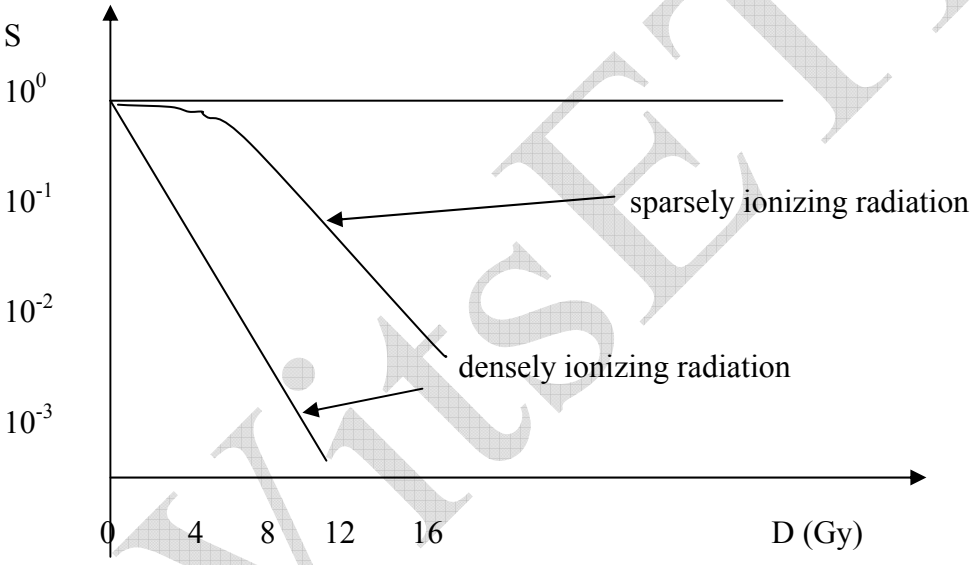

Figure 2.0: Typical survival curves for mammalian cells exposed to radiation

For densely ionizing radiation the survival data closely approximate a straight line from the origin[3]. In the case of sparsely ionizing radiations, the survival curve has a characteristic shape illustrated by the curve as labeled in Figure 2.0. At low doses there is an initial shoulder, followed by a portion which becomes straight, or almost straight on a semi-logarithmic plot[3,15].

Clonogenic survival is defined as the ability of a single cell to give rise to a colony of cells on a petri dish[15]. Clonogenic survival does not describe the continual existence of a single cell, but rather describes the ability of the cell to reproduce. On the other hand clonogenic or reproductive death is defined for purposes of radiation biology as the loss of the ability of a single cell to act as a progenitor (clone) for a significant line of offspring.

2.1 SINGLE HIT MODEL

Target theory originated from work with exponential dose response curves. It was assumed that each "hit" resulted in an inactivation, i.e., a "single-hit, single-target model".

BASIC ASSUMPTIONS OF THE MODEL[16]

1. Each cell has a single target.
2. Inactivation of the target kills the cell.

Irradiation of cells with high- linear energy transfer (LET) radiation produces linear survival curves. The relationship between the surviving fraction S and the dose D is then:

$$S = \exp(-\alpha D) \quad \textbf{2.0}$$

where : S is the number of surviving cells

- α is the slope , and
- D is the radiation dose delivered.

This relationship is more commonly represented as

$$S = \exp(-D / D_o) \quad \textbf{2.1}$$

by defining D_o as $1/\alpha$

when $D = D_o$,

$$S = \exp^{-1} = 0.37 \quad \textbf{2.2}$$

2.2 MULTI-TARGET SINGLE HIT SURVIVAL

A single-hit inactivation model is limited in applicability to radiation biology. The general extension of the target theory model that finds the widest applicability is the Multi-Target Single Hit. In this model it is assumed that a number of targets are present in each cell. One or more of these must be inactivated[16]. Each target has an equal probability of being hit. More explicitly, it is assumed that all target volumes are the same. This latter assumption may be the greatest weakness of the model[16].

ASSUMPTIONS OF THE MODEL

1. Each cell contains n distinct and identical targets
2. Each target can be inactivated by the passage of a charged particle (a hit).
3. Inactivation of a target is a sublethal event.
4. All n targets must be inactivated to kill the cell.
5. For a dose D_o there is on average one hit per target.

Therefore, for a dose D_o, the probability that a target is undamaged is $\exp(-D / D_o)$.
If the probability that a target survives is $S = \exp(-D / D_o)$, then the probability that the target is hit is :

$$P(h) = 1 - \exp(-D / D_o) \quad \textbf{2.3}$$

and the probability that all n targets are hit is

$$P(h) = (1 - \exp(-D / D_o))^n \quad \textbf{2.4}$$

Therefore the probability that all targets will not be hit, i.e., the probability of survival, is

$$S = 1 - (1 - \exp(-D / D_o))^n \quad \textbf{2.5}$$

2.3 MOLECULAR THEORY OF RADIATION ACTION

The model proposed by Chadwick and Leenhouts (1981), attempted to correct the deficiencies of the target theory models. It is known as the Linear-Quadratic (LQ) Model

by workers in the field[3,17]. The LQ model (also called the dual radiation action therapy) has two components:

1. The linear component: α-type damage

A double chromosome break is caused by the passage of a single charged particle for example, a high LET electron. This is equivalent to the single hit component of the target theory. From single –target single hit or multi-target, single hit model $S = e^{-D/Do}$. Replace 1/Do by α. Hence,

$$S = e^{-\alpha D} \quad \textbf{2.6}$$

2. The quadratic component: β-type damage

Two separate chromosomes breaks are caused by separate charged particles. The probability that one chromosome break will occur is linearly proportional to dose D. The probability that the other chromosome will be hit in an independent event is also proportional to dose D .The probability that both events will occur is therefore proportional to $e^{-\beta D^2}$. Hence,

$$S = e^{-\beta D^2} \quad \textbf{2.7}$$

When the two components are combined, we have

$$S = e^{-(\alpha D+\beta D^2)} \quad \textbf{2.8}$$

where

α represents the probability of α-type damage, which is irreparable.

β represents the probability that independent repairable, β-type events have combined to produce lethal events for example double chromosome breaks.

When using the linear-quadratic models for survival analysis, there are two components as mentioned before. The alpha component represents the initial slope, and the beta

component represents the terminal slope of the survival curve. The dose at which the alpha and beta components are equal is referred to as the alpha-beta ratio[3].