Journal of Theoretical Biology 394 (2016) 93–101

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Mathematical models of radiation action on living cells: From the target theory to the modern approaches. A historical and critical review

Larry Bodgi [a,b,f], Aurélien Canet [a,c], Laurent Pujo-Menjouet [c], Annick Lesne [d,e,f], Jean-Marc Victor [d,e,f], Nicolas Foray [a,f,*]

[a] Institut National de la Santé et de la Recherche Médicale (INSERM), UMR 1052, Radiobiology Group, Cancer Research Centre of Lyon, 69008 Lyon, France
[b] Université Saint-Joseph, Faculté des sciences, 1107-2050 Beyrouth, Liban
[c] Université Claude Bernard-Lyon 1, Institut Camille Jordan, 69622, Villeurbanne, France
[d] Centre National de la Recherche Scientifique (CNRS), UMR 7600, Laboratoire de Physique Théorique de la Matière Condensée, Université Pierre et Marie Curie-Paris 6, Sorbonne Universités, 75252 Paris, France
[e] Centre National de la Recherche Scientifique (CNRS), UMR 5535, Institut de Génétique Moléculaire de Montpellier, Université de Montpellier, 34293 Montpellier, France
[f] Centre National de la Recherche Scientifique (CNRS), GDR 3536, Nuclear Architecture and Dynamics, Université Pierre et Marie Curie-Paris 6, 75252 Paris, France

HIGHLIGHTS

- Several mathematical models were proposed to describe the survival curves of irradiated cells.
- The Linear-Quadratic model is the most used but its biological meaning is unknown.
- We revisit literature by providing clues for resolving the Linear-Quadratic model.

ARTICLE INFO

Article history:
Received 26 July 2015
Received in revised form
9 January 2016
Accepted 12 January 2016
Available online 22 January 2016

Keywords:
DSB repair
Ionising radiation
Models of radiation action
Cell survival
Radiosensitivity

ABSTRACT

Cell survival is conventionally defined as the capability of irradiated cells to produce colonies. It is quantified by the clonogenic assays that consist in determining the number of colonies resulting from a known number of irradiated cells. Several mathematical models were proposed to describe the survival curves, notably from the target theory. The Linear-Quadratic (LQ) model, which is to date the most frequently used model in radiobiology and radiotherapy, dominates all the other models by its robustness and simplicity. Its usefulness is particularly important because the ratio of the values of the adjustable parameters, α and β, on which it is based, predicts the occurrence of post-irradiation tissue reactions. However, the biological interpretation of these parameters is still unknown.

Throughout this review, we revisit and discuss historically, mathematically and biologically, the different models of the radiation action by providing clues for resolving the enigma of the LQ model.

1. Introduction

Cellular radiosensitivity was conventionally defined as the inability of irradiated cells to produce daughter cells (i.e. colonies). It is quantified by the clonogenic assays that consist in determining the number of colonies resulting from a given number of cells irradiated at a given dose. The survival fraction obeys a decreasing exponential-like law (it is generally plotted on a semi-log scale) with or without shoulder (Puck and Marcus, 1956). Several mathematical models, detailed below, were proposed to describe cell survival curves (Curtis, 1991). Interestingly, the hypotheses on which they are based reflect the conceptual advances in our understanding of the radiation response (Fig. 1):

– between the 1920s and the 1950s, the most extensively used cell survival models were directly derived from the target theory, such as the single-target single-hit, n-targets single-hit and n-hits n-targets models, including the so-called (n, D_0) model (Elkind and Whitmore, 1967).
– between the 1950s and the 1980s, the (n, D_0) model was used intensely. However, the evidence that the initial slope of the

* Corresponding author at: INSERM UMR 1052, Centre de Recherche en Cancérologie de Lyon, Groupe de Radiobiologie, 28 Rue Laennec, 69008 Lyon, France.

http://dx.doi.org/10.1016/j.jtbi.2016.01.018
0022-5193/

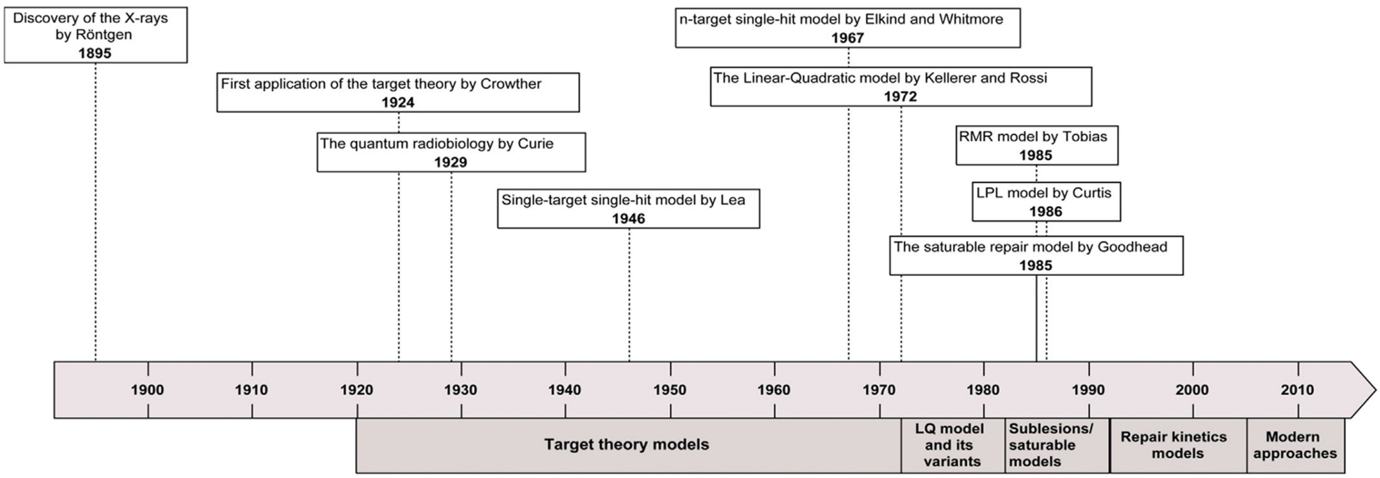

Fig. 1. Historical synopsis related to the cell survival models and their variants.

survival curve was not nil has significantly decreased its interest. In the early 1980s, the linear-quadratic (LQ) model was preferred because of its very good fitting qualities, but the empiric nature of its parameters, α and β, encouraged the authors to develop other models (Chadwick and Leenhouts, 1973).

– between the 80s and the 90s, more sophisticated models were proposed by introducing the notion of DNA damage repair but without leading to formulas simpler than the LQ model, nor providing a clear mechanistic explanation to the radiation-induced phenomena. It is notably the case of the Repair–MisRepair (RMR) (Tobias, 1985), the Lethal-Potentially Lethal (LPL) (Curtis, 1986), and the saturated repair models (Goodhead, 1985).
– since the 90s, while there is a lower infatuation towards the biostatistical models describing cell survival, radiobiologists started focusing on the description of the DNA damage repair kinetics linked to cell survival (Bodgi et al., 2013; Cucinotta et al., 2000; Foray et al., 2005; Gastaldo et al., 2008; Iliakis, 1991; Neumaier et al., 2012; Radivoyevitch et al., 1998; Sontag, 1997).

2. The target theory and its major related cell survival models

2.1. The genesis of the target theory

Funded by physicists, the target theory is based on two major principles:

– 1) *“radiation is considered to be a sequence of random projectiles;*
– 2) *the components of the cell are considered as the targets bombarded by these projectiles”* (Summers, 2011).

The target theory was first applied by Crowther in 1924 through an analysis of data from an experiment on chick embryo cells exposed to soft X-rays that was performed by Strangeways and Oakley in 1923 (Crowther, 1924; Strangeways and Oakley, 1923). In this case, the sensitive targets were hypothesized to be mitotic cells (Crowther, 1924). In 1929, Holweck[1] and Lacassagne obtained survival curves from bacillus irradiated by UV, X-rays or alpha-particles (Holweck, 1929; Lacassagne, 1929). Marie Curie analyzed the data and all these authors proposed the basis of the so-called *quantum radiobiology*: “*to destroy a bacillus it is necessary that its sensitive zone absorbs a minimal number s of quantas”* (Curie, 1929). From all these pioneering applications of the target theory, three important comments concerning *hits* and *targets* must be done:

– 1) The probability density function that was systematically applied to describe hits into sensitive cellular targets was a Poisson law.
– 2) The actual nature of the sensitive cellular targets was not consensual: they can be sub-populations of certain cells or some part of the nucleus.
– 3) The survival of irradiated cells was considered as the result of the absence of any hit on sensitive cells.

2.2. The basic ballistic models

2.2.1. The single-target single-hit model

It is the simplest application of the target theory. Directly derived from the hypotheses of Crowther and Curie, it was highlighted by Lea[2] at the end of 50’s throughout his book *“Actions of radiation action on living cells”* (Lea, 1946). The single-target single-hit model dominates with both its simplicity and robustness all the approaches leading to cell survival. It is based on the hypothesis that a single impact in the sensitive part is enough to kill the cell. By considering the Poisson probability to hit *k* times a target:

$$P(k) = \frac{m^k}{k!} e^{-m} \quad (1)$$

The probability of no impact is therefore:

$$P(0) = e^{-m} \quad (2)$$

[1] Born in 1889, Fernand Holweck became assistant of Marie Curie in 1912. During the First World War, he helped Paul Langevin in his works for detecting submarines by ultrasonic waves. Holweck developed a number of instruments like the most powerful vacuum-producer, a gravimetric pendulum, the first X-ray tube with successive stages of acceleration. Through his collaboration with Dr. Antoine Lacassagne, Holweck rediscovered, independently of the previous work by James Arnold Crowther, the quantic interpretation of the biological action of radiation on microorganisms. During the Second World War, he was actively engaged in defense work but was arrested, tortured and murdered by the Gestapo on December 14th, 1941, in a Paris prison.

(*footnote continued*)

[2] Douglas E. Lea (MA, PhD) was born in 1910 in Great Britain. During his career, he worked as a physicist at England's Strangeways Laboratory and as a reader in the Department of Radiobiology in the Department of Radiotherapeutics at Cambridge University. The majority of his work dealt with the effects of radiation on cells. Lea died in an accident in Cambridge, England, on June 16, 1947.