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Overview

Cell Kinetics

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ABSTRACT:
Cell kinetic concepts have pervaded radiation therapy since the early part of the 20th century and have been instrumental in the development of modern radiotherapy. In this review, the fundamental radiobiological concepts that have been developed based on cell kinetic knowledge will be revisited and discussed in the context of contemporary radiation therapy. This will include how the proliferation characteristics, variation in sensitivity during the cell cycle and the extent of radiation-induced cell cycle delay translate into a variable time for the expression of damage, how cell kinetics interacts with hypoxia and how the response to fractionated radiation schedules is influenced by cell kinetics in terms of repair, redistribution, reoxygenation and repopulation. The promise of combining radiation with new biologically targeted agents and the potential of non-invasive positron emission tomography imaging of proliferation are areas where cell kinetics will continue to influence radiotherapy practice. Wilson, G. D. (2007). *Clinical Oncology* 19, 370–384

Key words: Accelerated fractionation, cell cycle, cell kinetics, proliferation, radiosensitivity, repopulation

A Brief History of Cell Kinetics

The concept that proliferation kinetics of a tissue or tumour influences its response to treatment is fundamental in radiotherapy. As early as 1906, Bergonie and Tribondeau formulated their famous law, which stated that the radioresponsiveness of a tissue was directly related to its mitotic index. With time, the distinction has been made between radioresponsiveness and radiosensitivity as it became clear that although rapidly dividing tissues and tumours respond quickly to radiation they are not generally the most sensitive.

Cell kinetics takes its name from the Greek word, kinetikos, which means moving. Although mitosis and cell division had been studied since the early 1880s, the ability to study dynamic cell kinetics was realised at the beginning of the 1950s through the introduction of autoradiography [1]. Alma Howard and Stephen Pelc used bean root meristems labelled with ^{32}P to reveal that incorporation of the isotope into DNA occurs only within a certain limited period in the middle of interphase, such that the synthetic phase (S phase) was separated from the observable mitotic phase (M) by two gaps, G_1 and G_2 [2]. These seminal observations were made with relatively crude tools by modern standards, but this technique provided the impetus and opportunity to study many of the basic aspects of radiation and the cell cycle. Indeed, it had been known for most of the century [3] that radiation affects cell progression at very specific times before mitosis; it was autoradiography that provided the means to measure this unequivocally [4]. At the same time during the early 1960s, the simple, yet profoundly important, observation was made that mitotic cells were loosely attached to a glass surface and could be selectively removed by shaking [5]. The ability to produce a synchronised population of cells led to the discovery of the large variation in radiosensitivity throughout the cell cycle [6].

The ability to measure cell kinetics in experimental systems and human tumours stimulated enormous scientific interest in the ensuing decades and much of our current knowledge on the relationship between the proliferative status of cells and tissues and their response to radiotherapy was gained during this period [7–9]. In this review, the fundamental radiobiological concepts that have been developed based on cell kinetic knowledge will be revisited and discussed in the context of modern radiotherapy. This will include how the proliferation characteristics, variation in sensitivity during the cell cycle and the extent of radiation-induced cell cycle delay translate into a variable time for the expression of damage, how cell kinetics interacts with hypoxia and how the response to fractionated radiation schedules is influenced by cell kinetics in terms of repair, redistribution, reoxygenation and repopulation (Fig. 1).

Time Scales of Tissue and Tumour Response to Radiotherapy

Radiation is a unique cytotoxic agent by virtue of the fact that damage to DNA, inflicted at the time of irradiation, can remain latent for hours, days, weeks or months. This is

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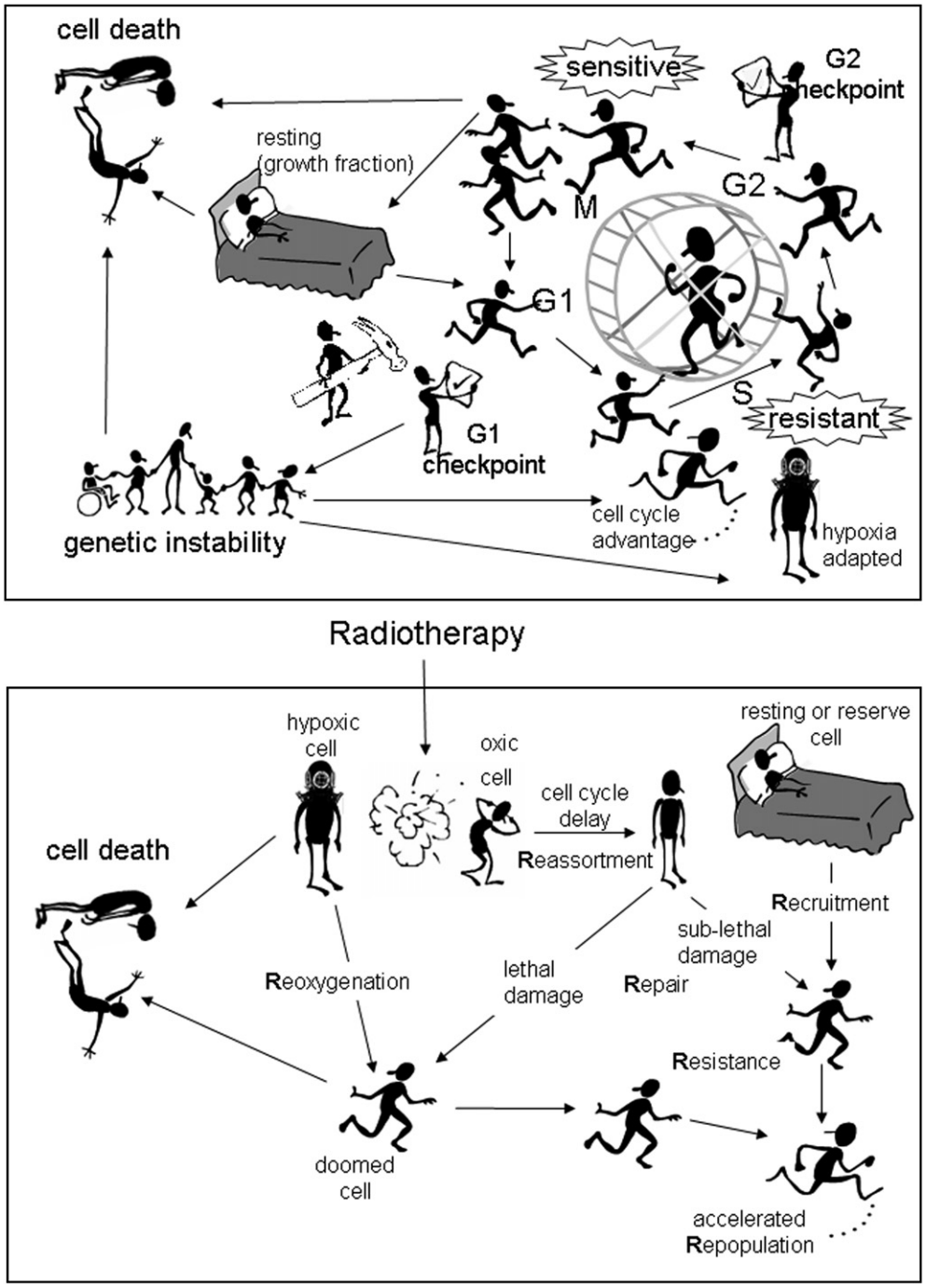

Fig. 1 — A schematic representation of the central role of cell kinetics in radiobiology applied to radiotherapy.

because, for the vast majority of normal tissues and tumours, cell death will not occur until the cell attempts to divide [10,11] and this is dependant on the proliferation characteristics of the tissue. In the intestinal epithelium, where the cell cycle time (T_c) is short (12—24 h), cell death occurs within hours, in skin (T_c 4 days) it may take a week, whereas in kidney (unknown T_c) it may be months. The time at which functional damage can be detected depends upon the time at which cell death occurs and the level of cell depletion that can be tolerated. The cell kinetic characteristics of normal tissues, not their intrinsic radiosensitivity, are closely correlated with the duration of the latent period before the onset of radiation-induced functional damage. This fundamental observation evolved from many labour-intensive studies using single-dose and fractionated irradiation of normal tissue models in experimental animals utilising a variety of ingenious functional end points. Figure 2 is adapted from Stewart and van der Kogel