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Mini-review

Variation, "evolution", immortality and genetic instabilities in tumour cells

L.P. Bignold

Division of Tissue Pathology, Institute of Medical and Veterinary Science, P.O. Box 14, Rundle Mall, Adelaide, SA 5068, Australia

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Abstract

The pathological characteristics of tumour cells often include variation of their histopathological features (i.e. "degrees of de-differentiation") between cases of the same tumour type and between different foci within individual tumours. Usually, only a few cell lines from tumours are immortal. Currently, somatic mutation, replicative infidelity of DNA and aneuploidy are suggested as alternative mechanisms of genomic disturbance underlying tumours. Nevertheless, apart from Hansemann's ideas of "anaplasia" and "de-differentiation" (proposed in the 1890s), and supposed "evolutionary themes" in cancer cell biology, little has been published concerning how histopathologic variation and immortality in tumour cells might arise. This paper reviews applications of the concepts of "variation" to tumours, including concepts of "evolution" and "cellular Darwinism". It is proposed that combinations of somatic mutation, DNA replicative infidelity and aneuploidy may explain the variabilities in tumours, and provide immortality in occasional tumour cells. A possible model involves (i) an initial somatic mutation causing reduced replicative fidelity of DNA, which could be variable in intensity, and thus give rise to variations between cases; (ii) a phase of replicative infidelity of DNA causing daughter cells lines to develop various abnormalities to different degrees, and hence provide for variation between areas of the same tumour. As a last event (iii) occasional asymmetric chromosomal distributions (aneuploidy) might "refresh" the ability of a daughter cell to replicate DNA faithfully causing them to become immortal. Thus extensively mutant and variable, hyperploid, and occasionally immortal cells might arise.

Keywords: Tumours; Histopathology; Genetics; Mitosis; Aneuploidy; DNA replication; Fidelity; Variation; Evolution; Geneic instability; Cellular Darwinism; Immortality

1. Introduction

Small, rounded "globules" in tumours were reported by Home in 1820 [1]. The existence of nuclei in tumour cells, and their characteristic continuous variation ("pleomorphism") of size and shape were documented by Müller in 1839 [2]. By the 1850s, differentiation (in the sense of specialisation) of somatic cells was distinguished from embryonic differentiation, and the nucleus was identified as the probable location of the cells' hereditary material [3–5]. Subsequently in the "histological period" of cancer research [5], Virchow [6] classified tumours according to their structural complexity, viz., – "histiocytoid-", "organoid-", "purely cellular-" and "teratomatous" types – all of them

E-mail address: leon.bignold@adelaide.edu.au

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supposedly due to some observable or inapparent "chronic irritation". Later, however, various "embryonal" theories of tumours emerged. This occurred when it was realised that even the most excessive growth rates of tumour cells do not exceed those in embryos, and also that in many tumours, nuclear:cytoplasmic ratios are increased to the levels which are common in embryonal cells. These theories were mainly (i) that tumour cells are "embryonic-like" (Royer-Collard); (ii) that they arise from embryonal cells which have failed to "mature" in particular parts of the body, but later proliferate, probably due to chronic irritation (Cohnheim); and (iii) that tumours are due to "reversal" of embryonic differentiation by somatic cells (Fol) [5,7].

The appreciation of histopathological variation in tumours really began in the mid-1850s with the discovery that particular tumour types derive from particular somatic cell types. This advance derived especially from the work of Thiersch, Waldeyer, Remak and others [5,7]. As a result, "histogenetic" classifications of tumours (i.e. according to their somatic cell-type-of-origin) emerged. These classifications rapidly superseded earlier ones, but nevertheless did not account for the differing degrees of the deviations which tumours show in comparison with their corresponding cell type of origin. These differing degrees were found to occur even within "benign" and "malignant" groupings of each histogenetic category [5,7,8].

Beginning in the 1870s, chromosomes, mitoses and many other previously unrecognised details of cell structure were discovered after the invention of apoachromatic lenses, appropriately refractive oils for oil immersion and other improvements to microscopes [9]. Continuous variabilities of abnormalities of chromosomes and their distributions in tumour cells were recognised without delay independently by Schottländer, Pfitzner, Cornil, Klebs and others [6,10]. Thus by the late 1880s, the opportunity existed for the analysis of the histopathologic variation in tumours in terms of disturbances of their cellular hereditary material.

2. Genetic mechanisms of biological variation

Variation within species of food plants and domestic animals has been of practical importance to all agricultural societies, and was discussed in the time of Aristotle and other Classical philosophers [11,12]. Beginning approximately in the early eighteenth century [13] mechanisms of variation came to be of particular interest because of the development of commercial breeding and hybridising of strains of plants and animals for economic purposes. By the second half of the nineteenth century, male and female gametes had been identified for almost all sexually reproducing organisms [14,15]. Darwin's theory of evolution of species (see below) – and the debates developing from it – further focussed attention on the types of variation in species. By the end of the nineteenth century, "discontinuous" variation (e.g. the either/or colour of peas in pods) and "continuous" variation (e.g. hair colour in European human populations) were clearly identified as major phenomena which a convincing theory of heredity had to explain [14–16]. Generally at this time, "discontinuous variation" was thought to be due to the presence or absence of a relevant hereditary factor (as was later found to be true for the determination of gender by sex-specific "X" and "Y" chromosomes). "Continuous variation" on the other hand, was explained in terms of variable total numbers of particular relevant, feature-specific hereditary factors ("gemmules" – Darwin; "plasmas" – Weismann; or "ids" – Nägeli: see [14–16]).

In the first half of the twentieth century, Mendel's description (re-discovered independently by Sutton and Boveri in 1902 – [17]) of "dominant" and "recessive" paired "factors" was found to explain most known instances of discontinuous variation in species. However, no Mendelian mechanisms of "continuous" variation were immediately obvious [16]. Only after much additional work in the first half of the twentieth century were various mechanisms discovered for continuous variation within the framework of Mendelian genetics. These mechanisms include the involvement of many different genes in a single trait (polygenic effects); variable numbers of copies of individual genes; multiple alleles of the same gene; variable "dominance" of certain alleles [18,19] and modifier genes [16,20]. Other mechanisms of continuous variation were recognised as gene actions which affect other genes (inferred from "reverse" mutations and "position effect" – reviewed [16,18,19,21]) and the effects on gene actions which arise from mobility of genomic structures (McClintock – see [22]).

In relation to evolution, genetic controversies involved mainly suggestions of "macro-mutational effects" (i.e. from one species to another – major discontinuous variation) as opposed to "micro-muta-