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What history tells us XXVIII. What is really new in the current evolutionary theory of cancer?

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1. Introduction

During recent years and months, the word 'evolution' has increasingly been included in the titles of articles describing the progressive transformations of tumours (see, for instance, Ding *et al.* 2012; Shah *et al.* 2012; Gerlinger *et al.* 2012). This evolutionary vision of cancer states that the development of a tumour is a process comparable to the evolution of organisms. It results from the occurrence of mutations, the formation of cellular clones characterized by the presence or absence of these mutations, and the possible competition between these clones. The speciation theory of cancer belongs to these evolutionary models of cancer (Vincent 2010; Duesberg *et al.* 2011). Its authors emphasize the importance of big chromosomal alterations in the emergence of the tumours. However, what precisely affords the comparison with species formation remains problematic.

The rise of the evolutionary vision of cancer is linked with the recent technological developments permitting the fast sequencing of full genomes, and with the advent of single-cell and deep sequencing, which allow a quantitative measure of the fraction of cells harbouring a specific mutation within a tumour. These studies have demonstrated intra-tumour genetic heterogeneity and helped to characterize the genetic relations between metastases and the tumours of origin, as well as the genetic variations associated with the relapses that often follow a treatment.

In parallel with the recent results, articles have been published to emphasize the importance of this new evolutionary theory of cancer, not only to understand the characteristics of tumours but also to find new therapeutic approaches to them, or to adapt present treatments to make them more effective (Merlo *et al.* 2006; Attolini and Michor 2009; Greaves and Maley 2012). All these authors see in the 1976 publication of Peter Nowell (Nowell 1976) the seminal description of cancer as an evolutionary process with clonal selection, although attention has only recently been paid to his model.

The fact that the incidence of cancer is controlled by natural selection is a different issue (Leroi *et al.* 2003), not discussed here, which is frequently confused with the previous one, and has received a lot of attention in Darwinian medicine.

In this contribution I will show that the history of the evolutionary vision of cancer is much more complex, and has deeper roots. Unveiling this complexity is also the way to turn the problem around and show what the study of cancer might bring to current evolutionary studies.

2. Nowell's contribution in 1976

The model of tumour evolution proposed by Nowell includes a first event called 'initiation' which transforms a normal cell into a neoplastic one that has a selective growth advantage over the adjacent normal cells. Regularly during the development of the tumour, new cellular clones are produced, some of which have a selective advantage. This finally leads to tumour cells with a 'unique, aneuploid karyotype associated with aberrant metabolic behavior and specific antigenic properties' (Nowell 1976, p 23). Nowell

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favours the hypothesis that variations have a genetic origin since some leukaemias have been recently associated with the occurrence of chromosomal translocations – see later. He also considers that the acquisition of an increased mutability is a prerequisite for the development of tumours. He shows how such an evolutionary vision of cancer explains the failures of therapeutics, and the necessity to focus efforts on the early stages of oncogenesis.

Although this article has much in common with the current evolutionary model of cancer, it also differs significantly from it. Nowell insists on the clonality of the tumours at every step of their progression. Tumours are homogeneous; variation and selection are only transient events. The idea that some mutations might be neutral is absent.

3. The article of Nowell in its context

Nowell was not the only one to propose an evolutionary model of cancer. A year before Nowell's article, John Cairns published an article in *Nature* entitled 'Mutation selection and the natural history of cancer' (Cairns 1975). Similar ideas were also developed in a popular book on cancer published 3 years later (Cairns 1978). For Cairns, 'cancer can be viewed as the operation of Darwinian selection among competing populations of dividing cells' (Cairns 1978, 151). What was important for Cairns was to emphasize that natural selection can be beneficial but also harmful. The evolutionary dimension of cancer was obvious to him, but it brought nothing to the explanation of cancer. What had to be understood were the mechanisms that prevent the cells that are the most sensitive to mutations, the stem cells with their long lives, from evolving into cancer cells: how the number of stem cells is limited, the possible occurrence of an asymmetric division of the genetic material in these cells, and the structural organization of stem cells that prevents competition for territory between them.

Reading Cairns and Nowell, one gets the feeling that the evolutionary vision of cancer was not so original, and in the case of Cairns, not explanatory. Interestingly, when Nowell was interviewed in 1998 on 'cancer genetics, cytogenetics' (Nowell *et al.* 1998), he did not mention his model. What he considered as his important contribution was the discovery in 1960 in chronic myelogenic leukaemia of a chromosomal modification (Nowell and Hungerford 1960), named the same year the 'Philadelphia chromosome'. The presence of this chromosomal marker in all the cells of patients demonstrated the clonal origin of the disease, and the role of genetic mutations. Similar results for other types of tumours were also obtained by the characterization of electrophoretic variants of sex-linked enzymes (Linder and Gartler 1965). Advances in cytogenetics at the end of the 1950s and beginning of the 1960s obviously supported the evolutionary conception of cancer by providing a firm proof for the occurrence of mutations (chromosomal translocations) in cancer, and by demonstrating the growth advantage of the clones harbouring them.

The simultaneity of the models of Cairns and Nowell can probably also be explained by two scientific developments that occurred during the same period. The first was the demonstration by Bruce Ames that carcinogens are mutagenic, either directly or indirectly through their transformation within organisms (Ames *et al.* 1973). The second was the rapid acceptance in immunology of the clonal selection model proposed by Burnet. The impact of the latter model expanded beyond immunology. Some biologists, as Jacques Monod, considered that the success of selective theories against instructive ones characterized modern biology (Monod 1972).

4. Evolution of tumours before Nowell and Cairns

The 1976 article was not Nowell's first attempt to describe the process of carcinogenesis. In 1965, he already published a paper in which he emphasized the role of mutations in radiation carcinogenesis (Cole and Nowell 1965). The subtitle 'the sequence of events' shows that the evolutionary model of cancer has its origin in the experimental study of tumour progression that was made possible by the discovery of chemical agents and viruses (Rous and Beard 1935) able to reproducibly induce cancer in animals. The word 'progression' that was widely used at that time simply meant that the characteristics of the tumours changed during their development through successive steps.

Leslie Foulds best described these different steps in a long series of articles (Foulds 1951, 1954, 1957). The term 'evolution' was sometimes used to describe them (see, for instance, Greene 1940). Evolution was considered as synonymous with progression in the colloquial sense, a usage that the 19th century philosopher Spencer would not have rejected. The fact that the cancer cells had a growth advantage was not denied. The possibility for a tumour to develop along different paths, and to reach different end-points, was also accepted. Nevertheless, for Foulds, tumour progression was independent of growth, and it could be abrupt or gradual (Foulds 1954), two ideas at odds with the Modern Synthesis of evolution.

The ideas that the progression of a tumour was, at least in part, a 'selective process', and that the cancerous cell 'struggles for existence', were present in models that apparently were very far from the current evolutionary model of cancer, such as the metabolic model of Otto Warburg (Warburg 1956). In this model the initial trigger to the development of a tumour is an injury to respiration. The requirement for the cell to activate glycolysis in order to maintain its energetic resources leads to its dedifferentiation, a process recurrently observed in cancers. This description of cancer may be called an 'evolutionary model of cancer' in the sense that it

describes the successive transformations of tumour cells, and does not exclude the possibility of a selection. But the evolution is not 'open', and the different steps are not linked to mutations of the genetic material.

The link between mutations and cancer had been proposed very early, at the beginning of the 20th century, by Theodor Boveri. He conceived the origin of cancer as the abnormal distribution of chromosomes during cell division, provoking a regression of the cell to an uncontrolled, egoistic behaviour (Boveri 1914, 1929 – the book was translated into English after his death; Manchester 1995; Manchester 1997).

The idea that cancer cells were unregulated cells that had escaped any control by the body was clearly at odds with the model that tumour cells evolve as organisms do. Once again, cancer was seen as the return to an ancestral, uncontrolled state, not the result of an open evolution.

This opposition probably explains why Wilhelm Roux did not propose an evolutionary model of cancer in his 1881 book on the fight of the parts within organisms (Roux 1881, 2012). This book was immediately well received, but rapidly forgotten. Roux proposed that a struggle between the different parts of the organism – molecules, cells, tissues and organs – took place during development. Somehow, he extended Darwinian competition to what happened within organisms during development. This competition of the different parts of the organism for resources was essential for the optimization of physiological adaptation. Since tumours also compete for food with the rest of the organism, it might have seemed appropriate to include them in the picture. Roux did not, because he considered that these cells had embryonic characteristics, as initially hypothesized by Julius Cohnheim, and were utterly unregulated. Their behaviour could not be compared to the well-regulated competition that took place during the development of organisms (Roux 1881, 2012, p 69).

5. Conclusion

The goal of this article was not to propose a full history of the theories of cancer, nor even of the evolutionary model of it, but simply to question the meaning and novelty of the current evolutionary models. In particular, I have not described other hypotheses and models that consider that genetic mutations are side phenomena in the formations of tumours, and see its true origin in the disorganization of the tissues (Soto and Sonnenschein 2011). In fact, the history of the evolutionary conception of cancer was no more or less tortuous and complex than the history of evolutionary theory itself. What is obvious is that the idea of an evolution of tumours, that cancer resulted from genetic variations, and the idea of a competition between tumour cells and the surrounding cells of the organism, were present during a large part of the 20th century. But there were other ideas, such as the vision of a regular progression in tumour development or the idea that cancer cells simply return to a primitive, uncontrolled state. These ideas prevented comparison of the evolution of a tumour with that of a population of organisms, and the use of the models of evolutionary theory to study tumour development. The present situation is different. Current technologies allow biologists to go beyond simple resemblances and to test experimentally whether or not a mutation in a tumour has been positively selected, by using tools developed in evolutionary biology (Bignell *et al.* 2010).

What is also obvious is that the current evolutionary theory of cancer is less constrained than was the Modern Synthesis. The role of neutral mutations is considered as important. Natural selection takes place, but its role can vary from one step to another during the development of the tumours. Tumour progression is a fact: there is no disagreement between the current evolutionary vision of cancer and the existence of 'hallmarks of cancer' (Hanahan and Weinberg 2011).

Catastrophic events, such as massive DNA and chromosomal rearrangements, are not excluded (Stephens *et al.* 2011; Rausch *et al.* 2012). The physiological state of the cancer cells can increase the occurrence of such catastrophic events (Chen *et al.* 2012). These observations are similar to those made in evolutionary biology. The importance of catastrophic events in the evolution of organisms was emphasized by Stephen Jay Gould, whereas it has been shown that microorganisms, under stress conditions, increase their rate of mutation to adapt to new environments. The relations between cancer cells and their environment are also complex: cancer cells participate in the construction of their environment (their niches).

The new evolutionary theory of cancer fully succeeds in linking the functional vision of cancer – with the progressive acquisition of new properties by cancer cells – and evolutionary scenarios. Thanks to the rapidly increasing abundance of molecular data, the field of cancer could serve as a model for other disciplines in which a similar link is looked for. Within Evo-Devo, the role of neutral mutations, the existence of a progression, i.e. the evidence for constraints that might guide the evolution of organisms, face much more opposition from 'traditional' evolutionary biologists who still consider that Modern Synthesis is a frame sufficient for the explanation of the evolution of organisms.

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