Carcino-Evo-Devo

Subjects: Biology
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The term “*carcino-evo-devo*” was used for the first time as a name for the theory of the evolutionary role of tumors. The new term was coined from two other terms: “*carcinoembryonic*” and “*evo-devo*”.

Keywords: carcinoembryonic ; evo-devo ; carcino-evo-devo ; evolution ; hereditary tumors

1. Introduction

The theory of the evolutionary role of hereditary tumors, or the *carcino-evo-devo* theory, was developed in order to explain the sources of additional cell masses, which were necessary for the origins of new cell types, tissues, and organs during the progressive evolution of multicellular organisms. The content of the theory has been published in the theoretical papers of the author [1][2][3][4][5][6][7][8][9][10][11][12][13] and as a monograph in English [14], Russian [15], and Chinese [16]. Many experimental papers from the author’s lab were devoted to the confirmation of nontrivial predictions of the *carcino-evo-devo* theory [17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39].

The basic statements of the *carcino-evo-devo* theory are the following:

- Tumor processes participate in the evolution of development;
- Hereditary tumors provide evolving multicellular organisms with extra cell masses for the expression of evolutionarily novel genes and gene combinations, and thereby participate in the origins of new cell types, tissues, and organs;
- Populations of tumor-bearing organisms served as transitional forms in progressive evolution;
- Tumors may be considered search engines for new gene combinations in the space of biological possibilities.

2. Preceding and Related Concepts

The term “*carcino-evo-devo*” was first introduced in [14], and it was used for the first time as a name for the theory of the evolutionary role of tumors in [9]. The new term was coined from two other terms: “*carcinoembryonic*” and “*evo-devo*”.

The term “*carcinoembryonic*” is used to designate embryonal proteins produced by tumor cells. The first examples of such proteins were alpha-fetoprotein [40][41] and carcinoembryonic antigen [42]. The concept of carcinoembryonic proteins was further developed in the concept of the convergence of embryonic and cancer signaling pathways [43][44][45][46]. These concepts point to molecular links between embryonal and tumor processes.

The abbreviation “*evo-devo*” corresponds to evolutionary developmental biology, which examines connections of normal individual development and evolution [47].

The *carcino-evo-devo* theory interconnects evolutionary, individual, and neoplastic development within one unified consideration. This theory studies the role of hereditary tumors in the evolution of development [9][14].

The previous concepts important for the *carcino-evo-devo* theory are the “embryonal rest” or “embryonal remnants” theory of cancer [48][49][50]; the morphological laws of the evolution of ontogenesis [51]; and the concept of neoplasia as a disease of differentiation [52].

Several previous ideas may be considered historical background for the theory, such as the idea of the role of “hopeful monsters” in evolution [53][54][55][56], and the idea of the positive role of viruses in evolution [57].

The *carcino-evo-devo* theory has been developing concurrently with Darwinian medicine [58], evolutionary epidemiology [59], and several branches of evolutionary oncology (e.g., the somatic evolution of tumor cells and selection in tumor cell populations [60][61][62], cancer selection [63], and the ecological hypothesis [64]). Comparative oncology has been in place since the 19th century (reviewed in [14]).

So, the *carcino-evo-devo* theory is deeply rooted in experimental oncology, developmental and evolutionary biology, and evolutionary medicine.

3. Tumor Features That Suggest the Role of Tumors in the Evolution of Organisms

3.1. Hereditary Tumors, like Any Hereditary Trait, Could Be Used in Evolution

Many tumors are hereditary. The high incidence of certain tumors in different strains of laboratory animals is a well-known phenomenon [14][65][66]. Cellular oncogenes and tumor suppressor genes are inherited as part of germline DNA and thus provide a genetic basis for tumor inheritance. The importance of germline mutations in cancer was recognized after the pioneering works of Alfred Knudson [67][68][69]. Twenty percent of cancer-associated mutations occur in the germline DNA, and ten percent are both somatic and germline mutations [70][71]. There is an inverse association between germline susceptibility risk and somatic genetic variation in human cancer [72][73]. Heritable epimutations associated with hereditary tumors (e.g., in Lynch syndrome) have also been described [74].

Tumor prevalence in wild and captive animals can reach a high percentage (e.g., >50% in Santa Catalina Island foxes) [75][76]. The highest cancer prevalence has been recorded in species or populations with low genetic diversity, which suggests that it may have a genetic basis (reviewed in [75]). In humans, increased cancer prevalence is also associated with reduced genetic diversity [77][78].

Hereditary cancer syndromes connected with inherited mutations in cancer predisposition genes, such as *MMR* or *BRCA* genes, account for a considerable proportion (up to 10%) of all cancers in humans [79][80][81][82]. The identification and clinical management of patients with such mutations became routine in modern oncology [83]. For the purpose of the discussion, it is important that hereditary cancer syndromes are much more frequent than noncancer hereditary syndromes, the classical genetic diseases (reviewed in [84]).

Any hereditary trait may be selected and may potentially be evolutionarily meaningful. The fact that many tumors are hereditary suggests that they might participate in the evolution of organisms. For example, germline mutations in *BRCA1* and *BRCA2* tumor suppressor genes increase the risk of breast and ovarian cancer in humans, and *Brca1* and *Brca2* genes participate in the embryonic development and differentiation of mammary glands in mice (reviewed in [10]).

When I talk about the evolutionary role of tumors, I mean hereditary tumors. More discussion on hereditary tumors may be found in [14].

3.2. The Widespread Occurrence of Tumors in Multicellular Organisms

Tumors are widespread throughout the phylogenetic tree [14]. New reviews on this topic, which appeared after the publication of the author's book, support the broad distribution of tumors across the tree of life [85][86].

Cellular oncogenes and tumor suppressor genes are also widespread throughout the phylogenetic tree, and many of them are ancient (oncogenes were already present in sponges).

3.3. A Considerable Portion of Tumors Never Kill Their Hosts

Many (maybe most) tumors never kill their hosts. Benign tumors are widespread in nature. They may represent more than half of all tumors [14]. New publications support this view: up to 80% of mammalian tumors are benign [76][87]. For example, in humans, benign lesions in the nasopharynx accounted for 75% of cases, with malignancies accounting for 25% [88].

At earlier stages of progression, tumors do not kill their hosts. Moreover, the overall direction of tumors in the early stages is toward regression [89]. Tumors can be selected for new functions at the early stages of progression [90].

The list of tumors that do not kill their hosts and could be used in evolution includes fetal, neonatal, and infantile tumors; carcinomas in situ and pseudodiseases; tumors that spontaneously regress; and sustainable tumor masses or extra cell masses in dynamic equilibrium with the organism [14].

When I talk about the evolutionary role of hereditary tumors, I mean benign tumors or tumors at the early stages of progression, or the kinds of tumors mentioned above, but not malignant tumors at the final stages of progression, which kill their hosts.

3.4. Tumors Have Many Features That Could Be Used in Evolution

Tumors are excessive cell masses that are not functionally necessary for the organism. Many unusual genes, which are not expressed in normal tissues, are expressed in tumors. There are also many unusual gene combinations expressed in tumors. Tumor cells can differentiate with the loss of malignancy, and tumors have morphogenetic potential.

All these features are much in demand in evolving multicellular organisms. However, they are not widely appreciated or discussed because the scientific community is more interested in tumors that kill the organism (i.e., malignant tumors, and the medical aspects of malignancy).

The data exist that tumors were indeed used in evolution (e.g., the positive selection of tumor-associated genes in primate evolution (reviewed in [14])), and examples of organs that possibly originated from tumors [9][10][11][14][91]. The placenta [9][10][14], the mammary gland and prostate [9][10], and mammalian adipose [11] are a few examples of organs that might have developed from tumors. In the author's book [14], further examples are covered, including the nitrogen-fixing root nodules of legumes, melanomatous cells and macromelanophores of *Xiphophorus* fish, hoods of Lionhead goldfish, and malignant papillomatosis and symbiovilli of voles.

New data suggest that tumors are connected with evolutionary adaptation [92] and the evolution rate [93].

3.5. "Nothing in Biology Makes Sense except in the Light of Evolution" [94]

Tumors are no exception to Dobzhansky's maxima, and biologists have started thinking about the place that tumors occupy in evolution. Several monographs have been published over the last decade on tumors and evolution [14][63][95][96]. Until very recently, the role of tumors in evolution was considered completely negative. The "tumors and evolution" relationships were studied mainly in a comparative biological context, or in the context of the evolution of tumor cells in tumor cell populations. However, the hereditary nature of many tumors, the widespread occurrence of tumors, the fact that a considerable proportion of tumors never kill their hosts, and tumor features that could be used in the evolution of multicellular organisms are all features that suggest that hereditary tumors could play some positive role in the evolution of host organisms.

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