ISSN 0006-2979, Biochemistry (Moscow), 2025, Vol. 90, No. 1, pp. 19-31 © Pleiades Publishing, Ltd., 2025.
Published in Russian in Biokhimiya, 2025, Vol. 90, No. 1, pp. 22-34.

REVIEW

Rethinking the Evolutionary Origin, Function, and Treatment of Cancer

Anatoly V. Lichtenstein

N. N. Blokhin National Medical Research Centre of Oncology, Ministry of Health of the Russian Federation, 115478 Moscow, Russia
alicht@mail.ru

Received September 29, 2024
Revised September 29, 2024
Accepted December 8, 2024

Abstract—Despite remarkable progress in basic oncology, practical results remain unsatisfactory. This discrepancy is partly due to the exclusive focus on processes within the cancer cell, which results in a lack of recognition of cancer as a systemic disease. It is evident that a wise balance is needed between two alternative methodological approaches: reductionism, which would break down complex phenomena into smaller units to be studied separately, and holism, which emphasizes the study of complex systems as integrated wholes. A consistent holistic approach has so far led to the notion of cancer as a special organ, stimulating debate about its function and evolutionary significance. This article discusses the role of cancer as a mechanism of purifying selection of the gene pool, the correlation between hereditary and sporadic cancer, the cancer interactome, and the role of metastasis in a lethal outcome. It is also proposed that neutralizing the cancer interactome may be a novel treatment strategy.

DOI: 10.1134/S0006297924603575

Keywords: war on cancer, cancer origin, cancer therapy, hallmarks of cancer, phenoptosis, cancer maleficence, neutralization strategy

In memory of V. P. Skulachev

INTRODUCTION

A recent publication, entitled “Why do Patients with Cancer Die?” [1], introduces a new “Roadmap Articles” series, which are intended to set the direction of the field and stimulate new avenues of thought and experimentation [2]. The text states that the specific causes of cancer mortality remain poorly understood, which presents a challenge for the development of novel treatment strategies. It is hoped that this line of experimentation will contribute to further advances in the field of cancer research and enhance clinical practice.

The same question (“What is the cause of death in cancer patients?”) had been asked 10 years earlier as an invitation to discuss the problems of the cancer–host relationships not only from a utilitarian-medical, but also from a biological perspective [3]. Indeed, understanding the mechanism of death may open up many possibilities for treating cancer by blocking the various stages of the process, whereas not knowing the mechanism condemns the physician to the only possible treatment strategy – physical destruction of the cancer cell. This is exactly what is happening today, however complex, difficult, and painful it may be. The predominant focus of mainstream research on intracellular processes [4], driven by the dominant desire to find deeply hidden vulnerabilities of the cancer cell, has led to the emergence of an increasing number of hallmarks of the cancer cell [5-8], without attempts to causally link them to the hallmarks of cancer disease (weakness and weight loss, chronic inflammation, anorexia, cachexia, anemia, coagulopathy, NETosis, systemic disorders, multiple organ failure) [9-18]. Today, as 20 years ago, “cancer research tends to focus on individual cellular mechanisms, almost to the near exclusion of what is happening in the organism as a whole” [19]. As a result, despite many remarkable advances in basic oncology, there is a growing sense that cancer research is on the verge of a paradigm shift [20]: practical advances remain limited,

the financial burden of treatment is a major concern, and despite some achievements in personalized therapy, surgery remains the main hope.

The discrepancy between the progress of experimental and practical cancer research appears to be, at least in part, a consequence of the triumph of a reductionist approach, which has resulted in a shift away from a holistic perspective [21]. (This conflict, as in the ancient Indian parable of the blind sages groping the elephant, is that a deep dive into the details of an object can lead away from understanding the object as a whole.) The holistic approach calls for an evolutionary perspective to be applied when examining the cancer–host relationships, a stance that is increasingly supported by recent evidence [22]. According to the traditional view, cancer arises as a consequence of the "design" constraints characteristic of evolution; it is the result of random mutations that lead to the disruption of multicellular cooperation, and cancer cells behave as "cheaters", reverting to their previous single-cell lifestyle [23, 24]. They selfishly replicate, compete for survival, spread between tissues and develop high reproductive success at the expense of Darwinian host fitness [25-27].

In contrast to the common opinion, two long-standing articles have presented the scientific community with an "elephant", discovering that cancer is in fact a special organ [28, 29]. Indeed, a tumor meets the formal definition of an organ as an "anatomically discrete collection of tissues integrated to perform specific functions" [28] and has the appropriate attributes – a complex hierarchical structure, often imitating normal tissue structure [30], the presence of stem and differentiated cells, regular stages of development, and integration with body systems. Cancer is extremely evolutionarily conservative: apparently a product of multicellularity that emerged about one billion years ago, it affects the majority of metazoan species [24, 27, 31].

The concept of "cancer as an organ" represents a radical departure from the traditional view. But although the term entered the scientific mainstream and it was even recognized that the complexity of tumor organ may exceed that of normal tissues [6], this paradigm shift went virtually unnoticed. This is probably because the first crucial step (the recognition of the fundamentally different nature of cancer than previously thought) was not followed by the second necessary and obvious one – a broad discourse on the function that gave rise to this organ and ensured its widespread distribution in the animal world (it is impossible to study an organ in isolation from its function and outside of an evolutionary perspective). This study aims to fill this gap in the existing literature by examining cancer as a mechanism of purifying selection of the gene pool, sporadic cancer as a by-product of hereditary cancer, and the maleficence of the cancer cell as its main hallmark. It is also suggested that neutralizing the cancer interactome may be a new treatment strategy.

EVOLUTIONARY ORIGIN OF CANCER

Early suggestions that cancer fulfils the function of purifying selection [22, 32-35] have not gained traction because most of the individuals that are killed by cancer are post-reproductive [36]. Nevertheless, the concept of "cancer as an organ" rekindles the debate, given that each organ must have an evolutionary rationale for its existence.

There are two types of cancer (hereditary and sporadic) and only the former is capable of negative selection. Hereditary cancer is the consequence of a germinal mutation in one of several dozens of "essential" genes [34, 37] involved in DNA repair, cell cycle regulation and cell-death pathways [38]. The germinal driver mutation, present in every cell of the body (including its germinal cells), represents a significant risk of cancer in its carrier. There are two main reasons for this: firstly, the cell transformation pathway is shortened, and secondly, the would-be cancer cell is initially located in a genetically compromised microenvironment (a situation that can be described as "criminal 'seeds' in criminogenic 'soil'" [39]). Thus, the germinal driver mutation poses a double danger: to the organism (high risk of highly penetrant, early onset cancer) and to the species (high probability of transmission to offspring). However, the realization of the former possibility eliminates the latter or, as Steve Sommer put it, "cancer kills the individual and saves the species" [33]. Inherited cancer syndromes with Mendelian dominant inheritance sharply reduce reproductive success of offspring [40] and purify the gene pool of the population from mutant alleles (frequency of predisposing alleles in population <1%) [41, 42].

Hereditary cancer is relatively rare [43-51], accounting for only a small fraction (~1%) of cancer incidence. So, the question arises how to explain the huge quantitative predominance of sporadic cancer, which is caused by somatic (not inherited) mutations, develops over decades and affects mainly people of post-reproductive age. Indeed, why kill old people who do not participate in evolution? The answer perhaps lies in the question itself: cancer kills old people precisely because they do not participate in evolution. In the spirit of the concept of antagonistic pleiotropy [40, 52, 53], one can assume that cancer acts in old age "by inertia", i.e., not out of necessity but because of the impossibility of getting rid of it (an old age that does not produce offspring is unable to evolve).

Thus, sporadic cancer is probably a by-product of hereditary cancer, and its enormous quantitative prevalence in *Homo sapiens* is a payment for artificially created comfortable life (with all its excesses and bad habits), for the constantly growing (~2.5 years per decade) human life-span due to changes in hygiene, public health, and nutrition [40], and for the aging-induced decrease in the transformational resistance of stem cells [54]. The lifetime risk of cancer in countries with an average life-span of 75-80 years is now ~50%, while by age 120 years it is predicted to be nearly 90% for men and over 70% for women [55]. High cancer incidence is probably a peculiarity of *Homo sapiens* that is far from typical representative of the animal world. In most other mammalian species cancer incidence rates are much lower [27, 56].

To illustrate the difference between hereditary and sporadic forms, consider the analogy of cancer with a self-destruction mechanism built into a missile; being hidden in the norm, it manifests itself in an accident. It may function as designed, preventing catastrophic consequences in the very rare events of a missile failure (hereditary cancer), or it may malfunction as a result of aging and deterioration of hardware components during storage. The longer the storage, the more frequent the failures (sporadic cancer). While in the first case the process is initiated by a small number of pre-determined deviations (and, accordingly, is realized by a few well-defined scenarios), in the second case it may result from a complex combination of multiple random defects accumulated over many years (and, accordingly, be realized in myriad manifestations). This analogy can explain the peculiarities of the mutational landscapes of hereditary and sporadic cancers [57-59] as well as many clinical, morphological and molecular differences between them.

The widespread use of NGS for hereditary testing has allowed experimental investigation of genotype-phenotype correlations among cancer patients [60]. Although the phenomenon of purifying selection by hereditary cancer seems undoubted, its efficacy has been questioned by recent studies. Contrary to expectations, it turned out that germline pathogenic variants (GPVs) in cancer predisposing genes are more common than anticipated [51, 61, 62]. Over a quarter of cancers in carriers of GPVs in high-penetrance genes lacked specific hallmarks of tumorigenesis associated with the germline allele [58]. This suggested that the tumors have developed independently of the underlying pathogenic germline allele and, therefore, GPVs are less penetrant than previously thought [63].

Several considerations can be made in this regard. First, determining the status of inherited mutations is complicated by the unexpectedly widespread occurrence of such phenomena as postzygotic mosaicism, aberrant clonal expansion, and clonal hematopoiesis [47, 64-76], which sometimes lead to misclassification. Second, in studying cancer as a biological phenomenon, *Homo sapiens* can hardly be considered as a representative experimental model. In the animal kingdom, cancer has a significant impact on the competitive abilities of individuals, susceptibility to pathogens, vulnerability to predators, and ability to disperse [31]. Habitat conditions, in turn, are thought to influence disease pathogenesis. Thousands of years of civilization have led to such radical changes in human lifestyle (hygiene, public health, nutrition) and environments that they may have significantly reduced the selective pressure of hereditary cancer. Third, a study was carried out recently to assess directly the evolutionary impact of childhood cancer on the human gene pool. It was found that pediatric cancer predisposition syndrome (pCPS) genes are highly constrained, indicating strong selective pressure on pCPS genes. The authors concluded that heritable childhood cancer leads to natural selection strong enough to significantly affect the present-day gene pool [77].

The hypothesis that “cancer kills the individual and saves the species” [33] leads to a highly counterintuitive view of cancer as an altruistic phenomenon. The basis of biological evolution, according to Darwin, is individual selection (i.e., selfishness). However, “perhaps the most remarkable aspect of evolution is its ability to generate co-operation in a competitive world” [78]. The contradiction between Darwin’s theory and the abundance of examples of co-operation and altruism in the wild was resolved a century later in inclusive fitness, kin selection [79, 80] and “selfish gene” [81] theories. Although theoretical debates are still ongoing (see [82-85]), the occurrence of co-operation and altruism in biological populations is unquestionable.

Altruism is most actively discussed in relation to the phenomenon of aging, starting from the early ideas of Weismann on programmed aging and ending with the concept of programmed and altruistic aging by Skulachev and others [86]. Within the latter, the concept of *phenoptosis* (the death of a whole organism) has been put forward. Similarly to cells from multicellular animals that have the capacity to activate a program of self-destruction (apoptosis) [87], it was suggested that “complex biological systems are equipped with programs that eliminate portions of the system that become dangerous or unnecessary for the system as a whole” [88]. One can suggest that cancer is a special case of phenoptosis. At the level of a multicellular organism, apoptosis counteracts the spread of essentially dangerous defects, but at the level of a population, cancer does this job. It is proposed that apoptosis and cancer are the first and second lines of defense of the biological hierarchy against harmful genetic damages.

DRIVER MUTATIONS TRIGGER A PRE-EXISTING EPIGENETIC PROGRAM

It is widely believed that cancer results from the accumulation of driver mutations and that it is as irreversible as the mutations themselves. While in the vast majority of cases, cancer is indeed preceded by mutations, they are not absolutely required for tumor formation. Tumor types with few or no mutations are known [89], while tumor reversion can occur despite their occurrence [90, 91]. It was established that epigenetic reprogramming itself can drive tumorigenesis [92] and that reversible inhibition of a gene-silencing mechanism mediated by Polycomb group proteins can by itself lead to irreversible tumor formation in fruit flies [93]. These facts are consistent with the idea of cancer as a change in normal cell differentiation [94]. In light of Waddington's epigenetic landscape concept, mutations of some essential genes cause epigenetic reprogramming, leading to a critical transition from the attractor state of a normal cell to the attractor state of a cancer cell [91]. In support of this view, the functional analysis of genetic alterations in several cancers (breast, colon, pancreatic cancer, and glioblastoma) showed that driver mutations varying widely between different cancer types hit the same major signaling pathways [95].

The latest data prompt a reconsideration of the role of mutations in carcinogenesis. In contrast with the prevailing view, it would appear that they are not the drivers of the stochastic process. Rather, they seem to act as the trigger for a pre-existing evolutionary conserved epigenetic program. The evident similarity between embryogenesis and tumorigenesis suggests oncofetal reprogramming that enable tumor cells to escape from immune responses, promote growth and metastasis [96]. The concept of driver mutations as a trigger for a conserved program of cancer trans-differentiation may reconcile the conflicting Somatic Mutation Theory (SMT) [97] that views cancer as a genetic cell-based disease, and the Tissue Organization Field Theory (TOFT) [98, 99] that posits cancer as a tissue-based disease caused by developmental errors.

CANCER AS A PROGRAMMED DEATH OF AN ORGANISM

Cancer as an organ must have a function, and it is obvious – it is killer function, which is realized in a step-by-step manner and has the features of programmed death of the organism [35, 100]. The term "cancerous transformation" denotes a more profound alteration than the mere acquisition of a number of phenotypic characteristics, such as unregulated cell division. It signifies a radical change in the social behavior of a cell, whereby a "creator" cell becomes a "destroyer" cell. If a normal cell maintains the homeostasis of the organism, a cancer cell, on the contrary, like a "zombie", subordinates the host's metabolism to its own needs [101], builds a "niche" [102, 103], provides itself with blood supply [104], energy supply [105] and innervation [8, 106, 107], forms a microenvironment and pre-metastatic niches [108-112], colonizes the organism [113] and, finally, kills it and itself.

Death of cancer patient is perceived as something so obvious, self-evident, and inherent to cancer that the killer function is not explicitly articulated, not given due attention and is absent from the current list of hallmarks of cancer. The conventional wisdom that cancer mortality is usually a consequence of metastasizing equates metastasizing with *maleficence*, i.e. the ability of a cancer cell to kill the organism (the term *maleficence* is used here to distinguish it from *malignancy*, commonly denoting malignant growth as a whole). It is obvious, however, that metastasizing and maleficence are properties that, although apparently closely related, are essentially different. The fact that the *NALCN* gene regulates non-malignant cell dissemination, divorcing metastasizing from tumorigenesis, is significant in this regard [114]. There is much evidence of the systemic changes that cause most cancer deaths, not metastases *per se* [1, 29, 115].

The maleficence seems to be precisely the "hallmark waiting to be recognized" [116] that establishes the functional link between tumor and host and to which all other hallmarks apparently play an auxiliary role. Cancer maleficence has a diverse toolbox that includes secreted factors, extracellular microvesicles, extracellular nucleic acids and neurogenic factors [8, 101, 117-133]; this arsenal, which can be termed the cancer interactome, is capable of affecting distant organs, causing various paraneoplastic syndromes [9-13, 101, 134-136]. It is clear that the interactomes of normal and cancer cells are essentially the same, since they share the same genome. Apparently, the processes that a normal cell uses to maintain homeostasis, a cancer cell directs, on the contrary, to homeostasis failure, leveraging them inadequately in time and/or place, in unacceptable concentrations and/or combinations. One such "dual-use" facility is the senescence-associated secretory phenotype (SASP), which is known to be a potent tumor suppressive mechanism in normal ageing, but also a pro-malignant factor in genotoxic stress-induced cells [121, 137, 138]. Perhaps the most significant component of cancer maleficence is chronic inflammation, which often precedes and always accompanies malignant transformation [96, 139-145]. As a fundamental protective mechanism designed to fight infections and heal wounds, "it is antagonistic to the homeostatic mechanisms of organism, thus accounting for inevitable disturbance

of many functions" [146]. Recently, the involvement of extracellular vesicle fusion with target cells in triggering systemic inflammation has been shown [147]. One of consequences of inflammation is neutrophil extracellular traps (NETs), a normal defense mechanism designed to trap and neutralize microbes, but capable, when chronically activated, of inducing multi-organ failure [17, 148-152]. Cachexia is also closely linked to the inflammatory process [153-155]. Recently, the involvement of the peripheral and central nervous system in the oncological process has been identified [8, 156-158].

NEUTRALIZATION OF CANCER INTERACTOME AS A TREATMENT STRATEGY

If cancer is viewed as a distinct organ, its development as a series of pre-determined events, and its lethal outcome as a result of specific maleficence, then an understanding of the unifying mechanism of this function is an essential prerequisite for the development of a successful treatment. The commonly accepted statement "cancer is not one, but many different diseases", which states the enormous variety of clinical manifestations of cancer, reflects the clinical point of view. However, the experimenter sees in this diversity a single, albeit multivariant, pathogenic mechanism.

Progress in the war on cancer is unsatisfactory for two main reasons. Firstly, cancer cells quickly learn to avoid the means of defeat and, after initial, often very significant losses, regain their former positions and go on the offensive [159]. Secondly, the essential relatedness of cancer and normal cells makes the treatment a form of "friendly fire" with attendant, sometimes unacceptable, losses. This situation prompts to consider alternatives to current cancer cell-killing approaches, such as adaptive therapy [160, 161], "disease tolerance as a defense" strategy [162, 163], cancer reversion strategy [91], and neutralization strategy based on "antidotes" rather than "poisons" [164]. In the latter case, it is proposed that military actions be reoriented from the organ itself to its function, or more specifically, to the cancer interactome. It is this "neutralization" strategy that humans employ in the fight against their external enemies (poisonous animals): instead of hopeless and disastrous attempts at total destruction of the animals themselves, effective and harmless poison-specific antidotes are used. Presumably, the cancer interactome-neutralizing strategy could have several advantages over the cancer-killing strategy: (i) it seems likely that such a treatment would be considerably less toxic; (ii) assuming that different cancers have a similar interactome, the cancer neutralization strategy can be reduced to a limited number of therapeutic procedures instead of extremely expensive individualized therapy; (iii) the cancer-neutralizing strategy could also find application in chemoprevention, which uses pharmacological agents to arrest carcinogenesis at its earliest stages [165]. Some known examples of neutralizing strategy include the use of non-steroidal anti-inflammatory drugs (NSAIDs) to ameliorate the symptoms and improve the well-being of cancer patients [166] and DNase I injections into experimental animals to inhibit NETosis-associated metastasis [148].

To develop an effective antidote, a detailed understanding of the mechanism of harmful action is required. In the case of cancer, this means thorough investigation of interactome-mediated interplay between tumor and distant tissues. It is of great importance to ascertain the degree of variability and specificity of both the cancer interactome itself and its tissue and metabolic targets. In this context, it is instructive to look at the experience of aging studies, which focus on the aging organism as a whole and use the full range of high-throughput 'omics' technologies to study molecular processes in different tissues at the genomic, epigenomic, transcriptomic, proteomic, and metabolomic levels [167-169]. It can be assumed that, as in the case of aging, where the insights gained have led to significant practical results [170], the holistic approach to the cancer-bearing organism will reveal the targetable vulnerabilities in the cancer maleficence.

Funding. This study was funded by N. N. Blokhin National Medical Research Center of Oncology.

Ethics approval and consent to participate. This work does not contain any studies involving human and animal subjects.

Conflict of interest. The author of this work declares that he has no conflict of interest.

REFERENCES

1. Boire, A., Burke, K., Cox, T. R., Guise, T., Jamal-Hanjani, M., Janowitz, T., Kaplan, R., Lee, R., Swanton, C., Vander Heiden, M. G., and Sahai, E. (2024) Why do patients with cancer die? *Nat. Rev. Cancer*, **24**, 578-589, https://doi.org/10.1038/s41568-024-00708-4.
2. Editorial (2024) The road less travelled, *Nat. Rev. Cancer*, **24**, 515, https://doi.org/10.1038/s41568-024-00720-8.
3. Lichtenstein, A. V. (2014) Cancer research: a hurdle race, *Biochemistry (Moscow)*, **79**, 385-390, https://doi.org/10.1134/S0006297914050010.
4. Laplane, L., and Maley, C. C. (2024) The evolutionary theory of cancer: challenges and potential solutions, *Nat. Rev. Cancer*, **24**, 718-733, https://doi.org/10.1038/s41568-024-00734-2.

5. Hanahan, D., and Weinberg, R. A. (2000) The hallmarks of cancer, *Cell*, **100**, 57-70, https://doi.org/10.1016/S0092-8674(00)81683-9.
6. Hanahan, D., and Weinberg, R. (2011) Hallmarks of cancer: the next generation, *Cell*, **144**, 646-674, https://doi.org/10.1016/j.cell.2011.02.013.
7. Hanahan, D. (2022) Hallmarks of cancer: new dimensions, *Cancer Discov.*, **12**, 31-46, https://doi.org/10.1158/2159-8290.CD-21-1059.
8. Hanahan, D., and Monje, M. (2023) Cancer hallmarks intersect with neuroscience in the tumor microenvironment, *Cancer Cell*, **41**, 573-580, https://doi.org/10.1016/j.ccell.2023.02.012.
9. Tisdale, M. J. (2002) Cachexia in cancer patients, *Nat. Rev. Cancer*, **2**, 862-871, https://doi.org/10.1038/nrc927.
10. Finora, K. (2003) Common paraneoplastic syndromes, *Clin. Tech. Small Anim. Pract.*, **18**, 123-126, https://doi.org/10.1053/svms.2003.36629.
11. Kim, H. L., Belldegrun, A. S., Freitas, D. G., Bui, M. H., Han, K. R., Dorey, F. J., and Figlin, R. A. (2003) Paraneoplastic signs and symptoms of renal cell carcinoma: implications for prognosis, *J. Urol.*, **170**, 1742-1746, https://doi.org/10.1097/01.ju.0000092764.81308.6a.
12. Mazzone, P. J., and Arroliga, A. C. (2003) Endocrine paraneoplastic syndromes in lung cancer, *Curr. Opin. Pulm. Med.*, **9**, 313-320, https://doi.org/10.1097/00063198-200307000-00012.
13. Posner, J. B. (2003) Immunology of paraneoplastic syndromes: overview, *Ann. N. Y. Acad. Sci.*, **998**, 178-186, https://doi.org/10.1196/annals.1254.018.
14. Spivak, J. L. (2005) The anaemia of cancer: death by a thousand cuts, *Nat. Rev. Cancer*, **5**, 543-555, https://doi.org/10.1038/nrc1648.
15. Rak, J., Klement, P., and Yu, J. (2006) Genetic determinants of cancer coagulopathy, angiogenesis and disease progression, *Vnitr. Lek.*, **52**, 135-138.
16. Rak, J., Yu, J. L., Luyendyk, J., and Mackman, N. (2006) Oncogenes, Trousseau syndrome, and cancer-related changes in the coagulome of mice and humans, *Cancer Res.*, **66**, 10643-10646, https://doi.org/10.1158/0008-5472.CAN-06-2350.
17. Jorch, S. K., and Kubes, P. (2017) An emerging role for neutrophil extracellular traps in noninfectious disease, *Nat. Med.*, **23**, 279-287, https://doi.org/10.1038/nm.4294.
18. Inoue, M., Nakashima, R., Enomoto, M., Koike, Y., Zhao, X., Yip, K., Huang, S. H., Waldron, J. N., Ikura, M., Liu, F. F., and Bratman, S. V. (2018) Plasma redox imbalance caused by albumin oxidation promotes lung-predominant NETosis and pulmonary cancer metastasis, *Nat. Commun.*, **9**, 5116, https://doi.org/10.1038/s41467-018-07550-x.
19. Leaf, C. (2004) Why we're losing the war on cancer (and how to win it), *Fortune*, **149**, 76-82, 84-86, 88.
20. Goldstein, I., Madar, S., and Rotter, V. (2012) Cancer research, a field on the verge of a paradigm shift? *Trends Mol. Med.*, **18**, 299-303, https://doi.org/10.1016/j.molmed.2012.04.002.
21. Yuzhalin, A. E. (2024) Redefining cancer research for therapeutic breakthroughs, *Br. J. Cancer*, **130**, 1078-1082, https://doi.org/10.1038/s41416-024-02634-6.
22. Lichtenstein, A. V. (2005) On evolutionary origin of cancer, *Cancer Cell Int.*, **5**, 5, https://doi.org/10.1186/1475-2867-5-5.
23. Bozic, I., and Nowak, M. A. (2013) Unwanted evolution, *Science*, **342**, 938-939, https://doi.org/10.1126/science.1247887.
24. Greaves, M. (2007) Darwinian medicine: a case for cancer, *Nat. Rev. Cancer*, **7**, 213-221, https://doi.org/10.1038/nrc2071.
25. Merlo, L. M. F., Pepper, J. W., Reid, B. J., and Maley, C. C. (2006) Cancer as an evolutionary and ecological process, *Nat. Rev. Cancer*, **6**, 924-935, https://doi.org/10.1038/nrc2013.
26. Aktipis, C. A., and Nesse, R. M. (2013) Evolutionary foundations for cancer biology, *Evol. Appl.*, **6**, 144-159, https://doi.org/10.1111/eva.12034.
27. Aktipis, C. A., Boddy, A. M., Jansen, G., Hibner, U., Hochberg, M. E., Maley, C. C., and Wilkinson, G. S. (2015) Cancer across the tree of life: cooperation and cheating in multicellularity, *Philos. Trans. R Soc. Lond. B Biol. Sci.*, **370**, 20140219, https://doi.org/10.1098/rstb.2014.0219.
28. Bissell, M. J., and Radisky, D. (2001) Putting tumours in context, *Nat. Rev. Cancer*, **1**, 46-54, https://doi.org/10.1038/35094059.
29. Egeblad, M., Nakasone, E. S., and Werb, Z. (2010) Tumors as organs: complex tissues that interface with the entire organism, *Dev. Cell*, **18**, 884-901, https://doi.org/10.1016/j.devcel.2010.05.012.
30. Perez-Losada, J., and Balmain, A. (2003) Stem-cell hierarchy in skin cancer, *Nat. Rev. Cancer*, **3**, 434-443, https://doi.org/10.1038/nrc1095.
31. Vittecoq, M., Roche, B., Daoust, S. P., Ducasse, H., Misse, D., Abadie, J., Labrut, S., Renaud, F., Gauthier-Clerc, M., and Thomas, F. (2013) Cancer: a missing link in ecosystem functioning? *Trends Ecol. Evol.*, **28**, 628-635, https://doi.org/10.1016/j.tree.2013.07.005.
32. Graham, J. (1992) *Cancer Selection: The New Theory of Evolution*, Aculeus Press, pp. 1-213.
33. Sommer, S. S. (1994) Does cancer kill the individual and save the species? *Hum. Mutat.*, **3**, 166-169, https://doi.org/10.1002/humu.1380030214.
34. Thomas, M. A., Weston, B., Joseph, M., Wu, W., Nekrutenko, A., and Tonellato, P. J. (2003) Evolutionary dynamics of oncogenes and tumor suppressor genes: higher intensities of purifying selection than other genes, *Mol. Biol. Evol.*, **20**, 964-968, https://doi.org/10.1093/molbev/msg110.
35. Lichtenstein, A. V. (2010) Cancer: evolutionary, genetic and epigenetic aspects, *Clin Epigenetics*, **1**, 85-100, https://doi.org/10.1007/s13148-010-0010-6.

36. Leroi, A. M., Koufopanou, V., and Burt, A. (2003) Opinion: cancer selection, *Nat. Rev. Cancer*, **3**, 226-231, https://doi.org/10.1038/nrc1016.
37. Rahman, N. (2014) Realizing the promise of cancer predisposition genes, *Nature*, **505**, 302-308, https://doi.org/10.1038/nature12981.
38. Frank, S. A. (2004) Genetic predisposition to cancer – insights from population genetics, *Nat. Rev. Genet.*, **5**, 764-772, https://doi.org/10.1038/nrg1450.
39. Lichtenstein, A. V. (2018) Genetic mosaicism and cancer: cause and effect, *Cancer Res.*, **78**, 1375-1378, https://doi.org/10.1158/0008-5472.CAN-17-2769.
40. Byars, S. G., and Voskarides, K. (2020) Antagonistic pleiotropy in human disease, *J. Mol. Evol.*, **88**, 12-25, https://doi.org/10.1007/s00239-019-09923-2.
41. Ponder, B. A. (2001) Cancer genetics, *Nature*, **411**, 336-341, https://doi.org/10.1038/35077207.
42. Yang, X., Kar, S., Antoniou, A. C., and Pharoah, P. D. P. (2023) Polygenic scores in cancer, *Nat. Rev. Cancer*, **23**, 619-630, https://doi.org/10.1038/s41568-023-00599-x.
43. Marsh, D. J., and Zori, R. T. (2002) Genetic insights into familial cancers – update and recent discoveries, *Cancer Lett.*, **181**, 125-164, https://doi.org/10.1016/S0304-3835(02)00023-X.
44. Frank, S. A. (2004) Inheritance of cancer, *Discov. Med.*, **4**, 396-400.
45. Nagy, R., Sweet, K., and Eng, C. (2004) Highly penetrant hereditary cancer syndromes, *Oncogene*, **23**, 6445-6470, https://doi.org/10.1038/sj.onc.1207714.
46. Lynch, H. T., Drescher, K., Knezetic, J., and Lanspa, S. (2014) Genetics, biomarkers, hereditary cancer syndrome diagnosis, heterogeneity and treatment: a review, *Curr. Treat. Options Oncol.*, **15**, 429-442, https://doi.org/10.1007/s11864-014-0293-5.
47. Coffee, B., Cox, H. C., Kidd, J., Sizemore, S., Brown, K., Manley, S., and Mancini-DiNardo, D. (2017) Detection of somatic variants in peripheral blood lymphocytes using a next generation sequencing multigene pan cancer panel, *Cancer Genet.*, **211**, 5-8, https://doi.org/10.1016/j.cancergen.2017.01.002.
48. Poliani, L., Greco, L., Barile, M., Dal, B. A., Bianchi, P., Basso, G., Giatti, V., Genuardi, M., Malesci, A., and Laghi, L. (2022) Canonical and uncanonical pathogenic germline variants in colorectal cancer patients by next-generation sequencing in a European referral center, *ESMO Open*, **7**, 100607, https://doi.org/10.1016/j.esmoop.2022.100607.
49. Chang, Y. S., Chao, D. S., Chung, C. C., Chou, Y. P., Chang, C. M., Lin, C. L., Chu, H. W., Chen, H. D., Liu, T. Y., Juan, Y. H., Chang, S. J., and Chang, J. G. (2023) Cancer carrier screening in the general population using whole-genome sequencing, *Cancer Med.*, **12**, 1972-1983, https://doi.org/10.1002/cam4.5034.
50. Garutti, M., Foffano, L., Mazzeo, R., Michelotti, A., Da, R. L., Viel, A., Miolo, G., Zambelli, A., and Puglisi, F. (2023) Hereditary cancer syndromes: a comprehensive review with a visual tool, *Genes (Basel)*, **14**, 1025, https://doi.org/10.3390/genes14051025.
51. Imyanitov, E. N., Kuligina, E. S., Sokolenko, A. P., Suspitsin, E. N., Yanus, G. A., Iyevleva, A. G., Ivantsov, A. O., and Aleksakhina, S. N. (2023) Hereditary cancer syndromes, *World J. Clin. Oncol.*, **14**, 40-68, https://doi.org/10.5306/wjco.v14.i2.40.
52. Williams, G. C. (1957) Pleiotropy, natural selection, and the evolution of senescence, *Evolution*, **11**, 398-411, https://doi.org/10.1111/j.1558-5646.1957.tb02911.x.
53. Austad, S. N., and Hoffman, J. M. (2018) Is antagonistic pleiotropy ubiquitous in aging biology? *Evol. Med. Public Health*, **2018**, 287-294, https://doi.org/10.1093/emph/eoy033.
54. Jassim, A., Rahrmann, E. P., Simons, B. D., and Gilbertson, R. J. (2023) Cancers make their own luck: theories of cancer origins, *Nat. Rev. Cancer*, **23**, 710-724, https://doi.org/10.1038/s41568-023-00602-5.
55. Ahmad, A. S., Ormiston-Smith, N., and Sasieni, P. D. (2015) Trends in the lifetime risk of developing cancer in Great Britain: comparison of risk for those born from 1930 to 1960, *Br. J. Cancer*, **112**, 943-947, https://doi.org/10.1038/bjc.2014.606.
56. Vincze, O., Colchero, F., Lemaitre, J. F., Conde, D. A., Pavard, S., Bieuville, M., Urrutia, A. O., Ujvari, B., Boddy, A. M., Maley, C. C., Thomas, F., and Giraudeau, M. (2022) Cancer risk across mammals, *Nature*, **601**, 263-267, https://doi.org/10.1038/s41586-021-04224-5.
57. Martincorena, I., Raine, K. M., Gerstung, M., Dawson, K. J., Haase, K., Van Loo, P., Davies, H., Stratton, M. R., and Campbell, P. J. (2017) Universal patterns of selection in cancer and somatic tissues, *Cell*, **171**, 1029-1041, https://doi.org/10.1016/j.cell.2017.09.042.
58. Srinivasan, P., Bandlamudi, C., Jonsson, P., Kemel, Y., Chavan, S. S., Richards, A. L., Penson, A. V., Bielski, C. M., Fong, C., Syed, A., Jayakumaran, G., Prasad, M., Hwee, J., Sumer, S. O., De Bruijn, I., Li, X., Gao, J., Schultz, N., Cambria, R., Galle, J., Mukherjee, S., Vijai, J., Cadoo, K. A., Carlo, M. I., Walsh, M. F., Mandelker, D., Ceyhan-Birsoy, O., Shia, J., Zehir, A., Ladanyi, M., Hyman, D. M., Zhang, L., Offit, K., Robson, M. E., Solit, D. B., Stadler, Z. K., Berger, M. F., and Taylor, B. S. (2021) The context-specific role of germline pathogenicity in tumorigenesis, *Nat. Genet.*, **53**, 1577-1585, https://doi.org/10.1038/s41588-021-00949-1.
59. Dolgin, E. (2020) Cancer genome complexity made simple, *Cancer Discov.*, **10**, 480, https://doi.org/10.1158/2159-8290.CD-NB2020-010.
60. Fortuno, C., Pesaran, T., Mester, J., Dolinsky, J., Yussuf, A., McGoldrick, K., James, P. A., and Spurdle, A. B. (2020) Genotype-phenotype correlations among TP53 carriers: Literature review and analysis of probands undergoing multi-gene panel testing and single-gene testing, *Cancer Genet.*, **248-249**, 11-17, https://doi.org/10.1016/j.cancergen.2020.09.002.

61. Amadou, A., Waddington Achatz, M. I., and Hainaut, P. (2018) Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome, *Curr. Opin. Oncol.*, **30**, 23-29, https://doi.org/10.1097/CCO.0000000000000423.
62. De Andrade, K. C., Mirabello, L., Stewart, D. R., Karlins, E., Koster, R., Wang, M., Gapstur, S. M., Gaudet, M. M., Freedman, N. D., Landi, M. T., Lemonnier, N., Hainaut, P., Savage, S. A., and Achatz, M. I. (2017) Higher-than-expected population prevalence of potentially pathogenic germline TP53 variants in individuals unselected for cancer history, *Hum. Mutat.*, **38**, 1723-1730, https://doi.org/10.1002/humu.23320.
63. Torrezan, G. T. (2023) Untangling the mechanisms of cancer predisposition, *Nat. Rev. Cancer*, **23**, 429, https://doi.org/10.1038/s41568-023-00577-3.
64. Riviere, J. B., Mirzaa, G. M., O'Roak, B. J., Beddaoui, M., Alcantara, D., Conway, R. L., St-Onge, J., Schwartzentruber, J. A., Gripp, K. W., Nikkel, S. M., Worthylake, T., Sullivan, C. T., Ward, T. R., Butler, H. E., Kramer, N. A., Albrecht, B., Armour, C. M., Armstrong, L., Caluseriu, O., Cytrynbaum, C., Drolet, B., Innes, A. M., Lauzon, J. L., Lin, A. E., Mancini, G. M., Meschino, W. S., Reggin, J. D., Saggar, A. K., Lerman-Sagie, T., Uyanik, G., Weksberg, R., Zirn, B., Beaulieu, C. L., Majewski, J., Bulman, D. E., O'Driscoll, M., Shendure, J., Graham, J. M., Jr., Boycott, K. M., and Dobyns, W. B. (2012) De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes, *Nat. Genet.*, **44**, 934-940, https://doi.org/10.1038/ng.2331.
65. Carethers, J. M., and Stoffel, E. M. (2015) Lynch syndrome and Lynch syndrome mimics: the growing complex landscape of hereditary colon cancer, *World J. Gastroenterol.*, **21**, 9253-9261, https://doi.org/10.3748/wjg.v21.i31.9253.
66. Huang, A. Y., Yang, X., Wang, S., Zheng, X., Wu, Q., Ye, A. Y., and Wei, L. (2018) Distinctive types of postzygotic single-nucleotide mosaicisms in healthy individuals revealed by genome-wide profiling of multiple organs, *PLoS Genet.*, **14**, e1007395, https://doi.org/10.1371/journal.pgen.1007395.
67. Weitzel, J. N., Chao, E. C., Nehoray, B., Van Tongeren, L. R., LaDuca, H., Blazer, K. R., Slavin, T., Facmg, D. A. B. M., Pesaran, T., Rybak, C., Solomon, I., Niell-Swiller, M., Dolinsky, J. S., Castillo, D., Elliott, A., Gau, C. L., Speare, V., and Jasperson, K. (2018) Somatic TP53 variants frequently confound germline testing results, *Genet. Med.*, **20**, 809-816, https://doi.org/10.1038/gim.2017.196.
68. Slavin, T. P., Coffee, B., Bernhisel, R., Logan, J., Cox, H. C., Marcucci, G., Weitzel, J., Neuhausen, S. L., and Mancini-DiNardo, D. (2019) Prevalence and characteristics of likely-somatic variants in cancer susceptibility genes among individuals who had hereditary pan-cancer panel testing, *Cancer Genet.*, **235-236**, 31-38, https://doi.org/10.1016/j.cancergen.2019.04.005.
69. Wright, C. F., Prigmore, E., Rajan, D., Handsaker, J., McRae, J., Kaplanis, J., Fitzgerald, T. W., FitzPatrick, D. R., Firth, H. V., and Hurles, M. E. (2019) Clinically-relevant postzygotic mosaicism in parents and children with developmental disorders in trio exome sequencing data, *Nat. Commun.*, **10**, 2985, https://doi.org/10.1038/s41467-019-11059-2.
70. Jaiswal, S., and Ebert, B. L. (2019) Clonal hematopoiesis in human aging and disease, *Science*, **366**, eaan4673, https://doi.org/10.1126/science.aan4673.
71. Mester, J. L., Jackson, S. A., Postula, K., Stettner, A., Solomon, S., Bissonnette, J., Murphy, P. D., Klein, R. T., and Hruska, K. S. (2020) Apparently heterozygous TP53 pathogenic variants may be blood limited in patients undergoing hereditary cancer panel testing, *J. Mol. Diagn.*, **22**, 396-404, https://doi.org/10.1016/j.jmoldx.2019.12.003.
72. Coffee, B., Cox, H. C., Bernhisel, R., Manley, S., Bowles, K., Roa, B. B., and Mancini-DiNardo, D. (2020) A substantial proportion of apparently heterozygous TP53 pathogenic variants detected with a next-generation sequencing hereditary pan-cancer panel are acquired somatically, *Hum. Mutat.*, **41**, 203-211, https://doi.org/10.1002/humu.23910.
73. Latorre-Pellicer, A., Gil-Salvador, M., Parenti, I., Lucia-Campos, C., Trujillano, L., Marcos-Alcalde, I., Arnedo, M., Ascaso, A., Ayerza-Casas, A., Antonanzas-Perez, R., Gervasini, C., Piccione, M., Mariani, M., Weber, A., Kanber, D., Kuechler, A., Munteanu, M., Khuller, K., Bueno-Lozano, G., Puisac, B., Gomez-Puertas, P., Selicorni, A., Kaiser, F. J., Ramos, F. J., and Pie, J. (2021) Clinical relevance of postzygotic mosaicism in Cornelia de Lange syndrome and purifying selection of NIPBL variants in blood, *Sci. Rep.*, **11**, 15459, https://doi.org/10.1038/s41598-021-94958-z.
74. Castillo, D., Yuan, T. A., Nehoray, B., Cervantes, A., Tsang, K. K., Yang, K., Sand, S. R., Mokhnatkin, J., Herzog, J., Slavin, T. P., Hyman, S., Schwartz, A., Ebert, B. L., Amos, C. I., Garber, J. E., and Weitzel, J. N. (2022) Clonal hematopoiesis and mosaicism revealed by a multi-tissue analysis of constitutional TP53 status, *Cancer Epidemiol. Biomarkers Prev.*, **31**, 1621-1629, https://doi.org/10.1158/1055-9965.EPI-21-1296.
75. Hendricks, L. A. J., Schuurs-Hoeijmakers, J., Spier, I., Haadsma, M. L., Eijkelenboom, A., Cremer, K., Mensenkamp, A. R., Aretz, S., Vos, J. R., and Hoogerbrugge, N. (2022) Catch them if you are aware: PTEN postzygotic mosaicism in clinically suspicious patients with PTEN Hamartoma Tumour Syndrome and literature review, *Eur. J. Med. Genet.*, **65**, 104533, https://doi.org/10.1016/j.ejmg.2022.104533.
76. Salazar, R., Arbeithuber, B., Ivankovic, M., Heinzl, M., Moura, S., Hartl, I., Mair, T., Lahnsteiner, A., Ebner, T., Shebl, O., Proll, J., and Tiemann-Boege, I. (2022)

Discovery of an unusually high number of *de novo* mutations in sperm of older men using duplex sequencing, *Genome Res.*, **32**, 499-511, https://doi.org/10.1101/gr.275695.121.

77. Stoltze, U. K., Foss-Skiftesvik, J., Hansen, T. O., Rasmussen, S., Karczewski, K. J., Wadt, K. A. W., and Schmiegelow, K. (2024) The evolutionary impact of childhood cancer on the human gene pool, *Nat. Commun.*, **15**, 1881, https://doi.org/10.1038/s41467-024-45975-9.
78. Nowak, M. A. (2006) Five rules for the evolution of cooperation, *Science*, **314**, 1560-1563, https://doi.org/10.1126/science.1133755.
79. Hamilton, W. D. (1964) The genetical evolution of social behaviour. I and II, *J. Theor. Biol.*, **7**, 17-52, https://doi.org/10.1016/0022-5193(64)90039-6.
80. Maynard-Smith, J. (1964) Group selection and kin selection, *Nature*, **201**, 1145-1147, https://doi.org/10.1038/2011145a0.
81. Dawkins, R. (1989) The Selfish Gene, *Oxford University Press*.
82. Nowak, M. A., Tarnita, C. E., and Wilson, E. O. (2010) The evolution of eusociality, *Nature*, **466**, 1057-1062, https://doi.org/10.1038/nature09205.
83. Abbot, P., Abe, J., Alcock, J., Alizon, S., Alpedrinha, J. A. C., Andersson, M., Andre, J. B., van Baalen, M., Balloux, F., Balshine, S., Barton, N., Beukeboom, L. W., Biernaskie, J. M., Bilde, T., Borgia, G., Breed, M., Brown, S., Bshary, R., Buckling, A., Burley, N. T., Burton-Chellew, M. N., Cant, M. A., Chapuisat, M., Charnov, E. L., Clutton-Brock, T., Cockburn, A., Cole, B. J., Colegrave, N., Cosmides, L., Couzin, I. D., Coyne, J. A., Creel, S., Crespi, B., Curry, R. L., Dall, S. R. X., Day, T., Dickinson, J. L., Dugatkin, L. A., Mouden, C. E., Emlen, S. T., Evans, J., Ferriere, R., Field, J., Foitzik, S., Foster, K., Foster, W. A., Fox, C. W., Gadau, J., Gandon, S., Gardner, A., Gardner, M. G., Getty, T., Goodisman, M. A. D., Grafen, A., Grosberg, R., Grozinger, C. M., Gouyon, P. H., Gwynne, D., Harvey, P. H., Hatchwell, B. J., Heinze, J., Helantera, H., Helms, K. R., Hill, K., Jiricny, N., Johnstone, R. A., Kacelnik, A., Kiers, E. T., Kokko, H., Komdeur, J., Korb, J., Kronauer, D., Kimmerli, R., Lehmann, L., Linksvayer, T. A., Lion, S., Lyon, B., Marshall, J. A. R., McElreath, R., Michalakis, Y., Michod, R. E., Mock, D., Monnin, T., Montgomerie, R., Moore, A. J., Mueller, U. G., Noë, R., Okasha, S., Pamilo, P., Parker, G. A., Pedersen, J. S., Pen, I., Pfennig, D., Queller, D. C., Rankin, D. J., Reece, S. E., Reeve, H. K., Reuter, M., Roberts, G., Robson, S. K. A., Roze, D., Rousset, F., Rueppell, O., Sachs, J. L., Santorelli, L., Schmid-Hempel, P., Schwarz, M. P., Scott-Phillips, T., Shellmann-Sherman, J., Sherman, P. W., Shuker, D. M., Smith, J., Spagna, J. C., Strassmann, B., Suarez, A. V., Sundstrom, L., Taborsky, M., Taylor, P., Thompson, G., Tooby, J., Tsutsui, N. D., Tsuji, K., Turillazzi, S., Ubeda, F., Vargo, E. L., Voelkl, B., Wenseleers, T., West, S. A., West-Eberhard, M. J., Westneat, D. F., Wiernasz, D. C., Wild, G., Wrangham, R., Young, A. J., Zeh, D. W., Zeh, J. A., and Zink, A. (2011) Inclusive fitness theory and eusociality, *Nature*, **471**, E1-E4, https://doi.org/10.1038/nature09831.
84. Kay, T., Keller, L., and Lehmann, L. (2020) The evolution of altruism and the serial rediscovery of the role of relatedness, *Proc. Natl. Acad. Sci. USA*, **117**, 28894-28898, https://doi.org/10.1073/pnas.2013596117.
85. Efferson, C., Bernhard, H., Fischbacher, U., and Fehr, E. (2024) Super-additive cooperation, *Nature*, **626**, 1034-1041, https://doi.org/10.1038/s41586-024-07077-w.
86. Longo, V. D., Mitteldorf, J., and Skulachev, V. P. (2005) Programmed and altruistic ageing, *Nat. Rev. Genet.*, **6**, 866-872, https://doi.org/10.1038/nrg1706.
87. Ameisen, J. C. (2002) On the origin, evolution, and nature of programmed cell death: a timeline of four billion years, *Cell Death. Differ.*, **9**, 367-393, https://doi.org/10.1038/sj.cdd.4400950.
88. Skulachev, V. P. (2001) The programmed death phenomena, aging, and the Samurai law of biology, *Exp. Gerontol.*, **36**, 995-1024, https://doi.org/10.1016/S0531-5565(01)00109-7.
89. Feinberg, A. P., Koldobskiy, M. A., and Gondor, A. (2016) Epigenetic modulators, modifiers and mediators in cancer aetiology and progression, *Nat. Rev. Genet.*, **17**, 284-299, https://doi.org/10.1038/nrg.2016.13.
90. Mintz, B., and Illmensee, K. (1975) Normal genetically mosaic mice produced from malignant teratocarcinoma cells, *Proc. Natl. Acad. Sci. USA*, **72**, 3585-3589, https://doi.org/10.1073/pnas.72.9.3585.
91. Shin, D., and Cho, K. H. (2023) Critical transition and reversion of tumorigenesis, *Exp. Mol. Med.*, **55**, 692-705, https://doi.org/10.1038/s12276-023-00969-3.
92. Ohnishi, K., Semi, K., Yamamoto, T., Shimizu, M., Tanaka, A., Mitsunaga, K., Okita, K., Osafune, K., Arioka, Y., Maeda, T., Soejima, H., Moriwaki, H., Yamanaka, S., Woltjen, K., and Yamada, Y. (2014) Premature termination of reprogramming *in vivo* leads to cancer development through altered epigenetic regulation, *Cell*, **156**, 663-677, https://doi.org/10.1016/j.cell.2014.01.005.
93. Parreno, V., Loubiere, V., Schuettengruber, B., Fritsch, L., Rawal, C. C., Erokhin, M., Gyorffy, B., Normanno, D., Di Stefano, M., Moreaux, J., Butova, N. L., Chiolo, I., Chetverina, D., Martinez, A. M., and Cavalli, G. (2024) Transient loss of Polycomb components induces an epigenetic cancer fate, *Nature*, **629**, 688-696, https://doi.org/10.1038/s41586-024-07328-w.
94. Sporn, M. B. (1996) The war on cancer, *Lancet*, **347**, 1377-1381, https://doi.org/10.1016/S0140-6736(96)91015-6.
95. Bessarabova, M., Pustovalova, O., Shi, W., Serebriyskaya, T., Ishkin, A., Polyak, K., Velculescu, V. E., Nikolskaya, T., and Nikolsky, Y. (2011) Functional

synergies yet distinct modulators affected by genetic alterations in common human cancers, *Cancer Res.*, **71**, 3471-3481, https://doi.org/10.1158/0008-5472.CAN-10-3038.

96. Sharma, A., Bleriot, C., Currenti, J., and Ginhoux, F. (2022) Oncofetal reprogramming in tumour development and progression, *Nat. Rev. Cancer*, **22**, 593-602, https://doi.org/10.1038/s41568-022-00497-8.
97. Greaves, M., and Maley, C. C. (2012) Clonal evolution in cancer, *Nature*, **481**, 306-313, https://doi.org/10.1038/nature10762.
98. Sonnenschein, C., Soto, A. M., Rangarajan, A., and Kulkarni, P. (2014) Competing views on cancer, *J. Biosci.*, **39**, 281-302, https://doi.org/10.1007/s12038-013-9403-y.
99. Soto, A. M., and Sonnenschein, C. (2011) The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory, *Bioessays*, **33**, 332-340, https://doi.org/10.1002/bies.201100025.
100. Lichtenstein, A. (2005) Cancer as a programmed death of an organism, *Biochemistry (Moscow)*, **70**, 1055-1064, https://doi.org/10.1007/s10541-005-0224-y.
101. Wang, G., Li, J., Bojmar, L., Chen, H., Li, Z., Tobias, G. C., Hu, M., Homan, E. A., Lucotti, S., Zhao, F., Posada, V., Oxley, P. R., Cioffi, M., Kim, H. S., Wang, H., Lauritzen, P., Boudreau, N., Shi, Z., Burd, C. E., Zippin, J. H., Lo, J. C., Pitt, G. S., Hernandez, J., Zambirinis, C. P., Hollingsworth, M. A., Grandgenett, P. M., Jain, M., Batra, S. K., DiMaio, D. J., Grem, J. L., Klute, K. A., Trippett, T. M., Egeblad, M., Paul, D., Bromberg, J., Kelsen, D., Rajasekhar, V. K., Healey, J. H., Matei, I. R., Jarnagin, W. R., Schwartz, R. E., Zhang, H., and Lyden, D. (2023) Tumour extracellular vesicles and particles induce liver metabolic dysfunction, *Nature*, **618**, 374-382, https://doi.org/10.1038/s41586-023-06114-4.
102. Barcellos-Hoff, M. H., Lyden, D., and Wang, T. C. (2013) The evolution of the cancer niche during multistage carcinogenesis, *Nat. Rev. Cancer*, **13**, 511-518, https://doi.org/10.1038/nrc3536.
103. Plaks, V., Kong, N., and Werb, Z. (2015) The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? *Cell Stem Cell*, **16**, 225-238, https://doi.org/10.1016/j.stem.2015.02.015.
104. Bergers, G., and Benjamin, L. E. (2003) Tumorigenesis and the angiogenic switch, *Nat. Rev. Cancer*, **3**, 401-410, https://doi.org/10.1038/nrc1093.
105. Luo, Y., Yoneda, J., Ohmori, H., Sasaki, T., Shimbo, K., Eto, S., Kato, Y., Miyano, H., Kobayashi, T., Sasahira, T., Chihara, Y., and Kuniyasu, H. (2014) Cancer usurps skeletal muscle as an energy repository, *Cancer Res.*, **74**, 330-340, https://doi.org/10.1158/0008-5472.CAN-13-1052.
106. Magnon, C., Hall, S. J., Lin, J., Xue, X., Gerber, L., Freedland, S. J., and Frenette, P. S. (2013) Autonomic nerve development contributes to prostate cancer progression, *Science*, **341**, 1236361, https://doi.org/10.1126/science.1236361.
107. Magnon, C., and Hondermarck, H. (2023) The neural addiction of cancer, *Nat. Rev. Cancer*, **23**, 317-334, https://doi.org/10.1038/s41568-023-00556-8.
108. Kaplan, R. N., Riba, R. D., Zacharoulis, S., Bramley, A. H., Vincent, L., Costa, C., MacDonald, D. D., Jin, D. K., Shido, K., Kerns, S. A., Zhu, Z., Hicklin, D., Wu, Y., Port, J. L., Altorki, N., Port, E. R., Ruggero, D., Shmelkov, S. V., Jensen, K. K., Rafii, S., and Lyden, D. (2005) VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche, *Nature*, **438**, 820-827, https://doi.org/10.1038/nature04186.
109. Kaplan, R. N., Rafii, S., and Lyden, D. (2006) Preparing the "soil": the premetastatic niche, *Cancer Res.*, **66**, 11089-11093, https://doi.org/10.1158/0008-5472.CAN-06-2407.
110. Peinado, H., Zhang, H., Matei, I. R., Costa-Silva, B., Hoshino, A., Rodrigues, G., Psaila, B., Kaplan, R. N., Bromberg, J. F., Kang, Y., Bissell, M. J., Cox, T. R., Giaccia, A. J., Erler, J. T., Hiratsuka, S., Ghajar, C. M., and Lyden, D. (2017) Pre-metastatic niches: organ-specific homes for metastases, *Nat. Rev. Cancer*, **17**, 302-317, https://doi.org/10.1038/nrc.2017.6.
111. De Visser, K. E., and Joyce, J. A. (2023) The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth, *Cancer Cell*, **41**, 374-403, https://doi.org/10.1016/j.ccell.2023.02.016.
112. Patras, L., Shaashua, L., Matei, I., and Lyden, D. (2023) Immune determinants of the pre-metastatic niche, *Cancer Cell*, **41**, 546-572, https://doi.org/10.1016/j.ccell.2023.02.018.
113. Karras, P., Black, J. R. M., McGranahan, N., and Marine, J. C. (2024) Decoding the interplay between genetic and non-genetic drivers of metastasis, *Nature*, **629**, 543-554, https://doi.org/10.1038/s41586-024-07302-6.
114. Rahrmann, E. P., Shorthouse, D., Jassim, A., Hu, L. P., Ortiz, M., Mahler-Araujo, B., Vogel, P., Paez-Ribes, M., Fatemi, A., Hannon, G. J., Iyer, R., Blundon, J. A., Lourenco, F. C., Kay, J., Nazarian, R. M., Hall, B. A., Zakharenko, S. S., Winton, D. J., Zhu, L., and Gilbertson, R. J. (2022) The NALCN channel regulates metastasis and nonmalignant cell dissemination, *Nat. Genet.*, **54**, 1827-1838, https://doi.org/10.1038/s41588-022-01182-0.
115. McAllister, S. S., and Weinberg, R. A. (2010) Tumor-host interactions: a far-reaching relationship, *J. Clin. Oncol.*, **28**, 4022-4028, https://doi.org/10.1200/JCO.2010.28.4257.
116. Bilder, D., Ong, K., Hsi, T. C., Adiga, K., and Kim, J. (2021) Tumour-host interactions through the lens of Drosophila, *Nat. Rev. Cancer*, **21**, 687-700, https://doi.org/10.1038/s41568-021-00387-5.
117. Wen, F., Shen, A., Choi, A., Gerner, E. W., and Shi, J. (2013) Extracellular DNA in pancreatic cancer

promotes cell invasion and metastasis, *Cancer Res.*, **73**, 4256-4266, https://doi.org/10.1158/0008-5472.CAN-12-3287.

118. Anastasiadou, E., and Slack, F. J. (2014) Malicious exosomes, *Science*, **346**, 1459-1460, https://doi.org/10.1126/science.aaa4024.
119. Ayala, G. E., Dai, H., Powell, M., Li, R., Ding, Y., Wheeler, T. M., Shine, D., Kadmon, D., Thompson, T., Miles, B. J., Ittmann, M. M., and Rowley, D. (2008) Cancer-related axonogenesis and neurogenesis in prostate cancer, *Clin. Cancer Res.*, **14**, 7593-7603, https://doi.org/10.1158/1078-0432.CCR-08-1164.
120. Balkwill, F. (2004) Cancer and the chemokine network, *Nat. Rev. Cancer*, **4**, 540-550, https://doi.org/10.1038/nrc1388.
121. Coppe, J. P., Patil, C. K., Rodier, F., Sun, Y., Munoz, D. P., Goldstein, J., Nelson, P. S., Desprez, P. Y., and Campisi, J. (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor, *PLoS Biol.*, **6**, 2853-2868, https://doi.org/10.1371/journal.pbio.0060301.
122. Gusachenko, O. N., Zenkova, M. A., and Vlassov, V. V. (2013) Nucleic acids in exosomes: disease markers and intercellular communication molecules, *Biochemistry (Moscow)*, **78**, 1-7, https://doi.org/10.1134/S000629791301001X.
123. Kharaziha, P., Ceder, S., Li, Q., and Panaretakis, T. (2012) Tumor cell-derived exosomes: A message in a bottle, *Biochim. Biophys. Acta*, **1826**, 103-111, https://doi.org/10.1016/j.bbcan.2012.03.006.
124. Khwaja, F. W., Svoboda, P., Reed, M., Pohl, J., Pyrzynska, B., and Van Meir, E. G. (2006) Proteomic identification of the wt-p53-regulated tumor cell secretome, *Oncogene*, **25**, 7650-7661, https://doi.org/10.1038/sj.onc.1209969.
125. Kim, S., Takahashi, H., Lin, W. W., Descargues, P., Grivennikov, S., Kim, Y., Luo, J. L., and Karin, M. (2009) Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis, *Nature*, **457**, 102-106, https://doi.org/10.1038/nature07623.
126. Kulbe, H., Levinson, N. R., Balkwill, F., and Wilson, J. L. (2004) The chemokine network in cancer – much more than directing cell movement, *Int. J. Dev. Biol.*, **48**, 489-496, https://doi.org/10.1387/ijdb.041814hk.
127. Kulbe, H., Thompson, R., Wilson, J. L., Robinson, S., Hagemann, T., Fatah, R., Gould, D., Ayhan, A., and Balkwill, F. (2007) The inflammatory cytokine tumor necrosis factor-alpha generates an autocrine tumor-promoting network in epithelial ovarian cancer cells, *Cancer Res.*, **67**, 585-592, https://doi.org/10.1158/0008-5472.CAN-06-2941.
128. Moller, A., and Lobb, R. J. (2020) The evolving translational potential of small extracellular vesicles in cancer, *Nat. Rev. Cancer*, **20**, 697-709, https://doi.org/10.1038/s41568-020-00299-w.
129. Nikitina, I. G., Sabirova, E. Yu., Karpov, V. L., Lisitsyn, N. A., and Beresten, S. F. (2013) The role of exosomes and microvesicules in carcinogenesis, *Mol. Biol. (Mosk)*, **47**, 767-773, https://doi.org/10.1134/S0026893313050166.
130. Rak, J. (2013) Extracellular vesicles – biomarkers and effectors of the cellular interactome in cancer, *Front. Pharmacol.*, **4**, 21, https://doi.org/10.3389/fphar.2013.00021.
131. Skryabin, G. O., Komelkov, A. V., Zhordania, K. I., Bagrov, D. V., Vinokurova, S. V., Galetsky, S. A., Elkina, N. V., Denisova, D. A., Enikeev, A. D., and Tchevkina, E. M. (2022) Extracellular vesicles from uterine aspirates represent a promising source for screening markers of gynecologic cancers, *Cells*, **11**, 1064, https://doi.org/10.3390/cells11071064.
132. Wels, J., Kaplan, R. N., Rafii, S., and Lyden, D. (2008) Migratory neighbors and distant invaders: tumor-associated niche cells, *Genes Dev.*, **22**, 559-574, https://doi.org/10.1101/gad.1636908.
133. Rak, J. (2015) Cancer: organ-seeking vesicles, *Nature*, **527**, 312-314, https://doi.org/10.1038/nature15642.
134. Darnell, R. B., and Posner, J. B. (2003) Paraneoplastic syndromes involving the nervous system, *N. Engl. J. Med.*, **349**, 1543-1554, https://doi.org/10.1056/NEJMra023009.
135. Sato, K., Onuma, E., Yocum, R. C., and Ogata, E. (2003) Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody, *Semin. Oncol.*, **30**, 167-173, https://doi.org/10.1053/j.seminoncol.2003.08.019.
136. Yamada, G., Ohguro, H., Aketa, K., Itoh, T., Shijubo, N., Takahashi, H., Fujiwara, O., Satoh, M., Ohtsuka, K., and Abe, S. (2003) Invasive thymoma with paraneoplastic retinopathy, *Hum. Pathol.*, **34**, 717-719, https://doi.org/10.1016/S0046-8177(03)00183-7.
137. Campisi, J. (2013) Aging, cellular senescence, and cancer, *Annu. Rev. Physiol.*, **75**, 685-705, https://doi.org/10.1146/annurev-physiol-030212-183653.
138. Faget, D. V., Ren, Q., and Stewart, S. A. (2019) Unmasking senescence: context-dependent effects of SASP in cancer, *Nat. Rev. Cancer*, **19**, 439-453, https://doi.org/10.1038/s41568-019-0156-2.
139. Dvorak, H. F. (1986) Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing, *N. Engl. J. Med.*, **315**, 1650-1659, https://doi.org/10.1056/NEJM198612253152606.
140. Balkwill, F., and Mantovani, A. (2001) Inflammation and cancer: back to Virchow? *Lancet*, **357**, 539-545, https://doi.org/10.1016/S0140-6736(00)04046-0.
141. Coussens, L. M., and Werb, Z. (2002) Inflammation and cancer, *Nature*, **420**, 860-867, https://doi.org/10.1038/nature01322.
142. Mantovani, A., Allavena, P., Sica, A., and Balkwill, F. (2008) Cancer-related inflammation, *Nature*, **454**, 436-444, https://doi.org/10.1038/nature07205.

143. Coussens, L. M., Zitvogel, L., and Palucka, A. K. (2013) Neutralizing tumor-promoting chronic inflammation: a magic bullet? *Science*, **339**, 286-291, https://doi.org/10.1126/science.1232227.
144. Grivennikov, S. I., Greten, F. R., and Karin, M. (2010) Immunity, inflammation, and cancer, *Cell*, **140**, 883-899, https://doi.org/10.1016/j.cell.2010.01.025.
145. Abu-Remaileh, M., Bender, S., Raddatz, G., Ansari, I., Cohen, D., Gutekunst, J., Musch, T., Linhart, H., Breiling, A., Pikarsky, E., Bergman, Y., and Lyko, F. (2015) Chronic inflammation induces a novel epigenetic program that is conserved in intestinal adenomas and in colorectal cancer, *Cancer Res.*, **75**, 2120-2130, https://doi.org/10.1158/0008-5472.CAN-14-3295.
146. Okin, D., and Medzhitov, R. (2012) Evolution of inflammatory diseases, *Curr. Biol.*, **22**, R733-R740, https://doi.org/10.1016/j.cub.2012.07.029.
147. Papareddy, P., Tapken, I., Kroh, K., Varma Bhongir, R. K., Rahman, M., Baumgarten, M., Cim, E. I., Gyorffy, L., Smeds, E., Neumann, A., Veerla, S., Olinder, J., Thorlacus, H., Ryden, C., Bartakova, E., Holub, M., and Herwald, H. (2024) The role of extracellular vesicle fusion with target cells in triggering systemic inflammation, *Nat. Commun.*, **15**, 1150, https://doi.org/10.1038/s41467-024-45125-1.
148. Hawes, M. C., Wen, F., and Elquza, E. (2015) Extracellular DNA: a bridge to cancer, *Cancer Res.*, **75**, 4260-4264, https://doi.org/10.1158/0008-5472.CAN-15-1546.
149. Cedervall, J., Zhang, Y., Huang, H., Zhang, L., Femel, J., Dimberg, A., and Olsson, A. K. (2015) Neutrophil extracellular traps accumulate in peripheral blood vessels and compromise organ function in tumor-bearing animals, *Cancer Res.*, **75**, 2653-2662, https://doi.org/10.1158/0008-5472.CAN-14-3299.
150. Cedervall, J., Zhang, Y., and Olsson, A. K. (2016) Tumor-induced NETosis as a risk factor for metastasis and organ failure, *Cancer Res.*, **76**, 4311-4315, https://doi.org/10.1158/0008-5472.CAN-15-3051.
151. Bonaventura, A., Liberale, L., Carbone, F., Vecchie, A., Diaz-Canestro, C., Camici, G., Montecucco, F., and Dallegri, F. (2018) The pathophysiological role of neutrophil extracellular traps in inflammatory diseases, *Thromb. Haemost.*, **118**, 6-27, https://doi.org/10.1160/TH17-09-0630.
152. Yang, L., Liu, Q., Zhang, X., Liu, X., Zhou, B., Chen, J., Huang, D., Li, J., Li, H., Chen, F., Liu, J., Xing, Y., Chen, X., Su, S., and Song, E. (2020) DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25, *Nature*, **583**, 133-138, https://doi.org/10.1038/s41586-020-2394-6.
153. McGovern, J., Dolan, R. D., Skipworth, R. J., Laird, B. J., and McMillan, D. C. (2022) Cancer cachexia: a nutritional or a systemic inflammatory syndrome? *Br. J. Cancer*, **127**, 379-382, https://doi.org/10.1038/s41416-022-01826-2.
154. Rounis, K., Makrakis, D., Gioulbasanis, I., Ekman, S., De, P. L., Mavroudis, D., and Agelaki, S. (2022) Cancer cachexia and antitumor immunity: common mediators and potential targets for new therapies, *Life (Basel)*, **12**, 880, https://doi.org/10.3390/life12060880.
155. Maccio, A., Madeddu, C., Lai, E., and Scartozzi, M. (2023) Cancer cachexia and chronic inflammation: an unbreakable bond, *Br. J. Cancer*, **128**, 1609-1610, https://doi.org/10.1038/s41416-023-02200-6.
156. Silverman, D. A., Martinez, V. K., Dougherty, P. M., Myers, J. N., Calin, G. A., and Amit, M. (2021) Cancer-associated neurogenesis and nerve-cancer cross-talk, *Cancer Res.*, **81**, 1431-1440, https://doi.org/10.1158/0008-5472.CAN-20-2793.
157. Wang, H., Zheng, Q., Lu, Z., Wang, L., Ding, L., Xia, L., Zhang, H., Wang, M., Chen, Y., and Li, G. (2021) Role of the nervous system in cancers: a review, *Cell Death Discov.*, **7**, 76, https://doi.org/10.1038/s41420-021-00450-y.
158. Zahalka, A. H., and Frenette, P. S. (2020) Nerves in cancer, *Nat. Rev. Cancer*, **20**, 143-157, https://doi.org/10.1038/s41568-019-0237-2.
159. Hanahan, D. (2014) Rethinking the war on cancer, *Lancet*, **383**, 558-563, https://doi.org/10.1016/S0140-6736(13)62226-6.
160. Gatenby, R. A., Silva, A. S., Gillies, R. J., and Frieden, B. R. (2009) Adaptive therapy, *Cancer Res.*, **69**, 4894-4903, https://doi.org/10.1158/0008-5472.CAN-08-3658.
161. Jansen, G., Gatenby, R., and Aktipis, C. A. (2015) Opinion: control vs. eradication: applying infectious disease treatment strategies to cancer, *Proc. Natl. Acad. Sci. USA*, **112**, 937-938, https://doi.org/10.1073/pnas.1420297111.
162. Medzhitov, R., Schneider, D. S., and Soares, M. P. (2012) Disease tolerance as a defense strategy, *Science*, **335**, 936-941, https://doi.org/10.1126/science.1214935.
163. Rao, S., and Ayres, J. (2017) Resistance and tolerance defenses in cancer: Lessons from infectious diseases, *Semin. Immunol.*, **32**, 61, https://doi.org/10.1016/j.smim.2017.08.004.
164. Lichtenstein, A. V. (2018) Strategies of the war on cancer: to kill or to neutralize? *Front. Oncol.*, **8**, 667, https://doi.org/10.3389/fonc.2018.00667.
165. Sporn, M. B., and Suh, N. (2002) Chemoprevention: an essential approach to controlling cancer, *Nat. Rev. Cancer*, **2**, 537-543, https://doi.org/10.1038/nrc844.
166. Roxburgh, C. S. D., and McMillan, D. C. (2014) Cancer and systemic inflammation: treat the tumour and treat the host, *Br. J. Cancer*, **110**, 1409-1412, https://doi.org/10.1038/bjc.2014.90.
167. Valdes, A. M., Glass, D., and Spector, T. D. (2013) Omics technologies and the study of human ageing, *Nat. Rev. Genet.*, **14**, 601-607, https://doi.org/10.1038/nrg3553.

168. Gurkar, A. U., Gerencser, A. A., Mora, A. L., Nelson, A. C., Zhang, A. R., Lagnado, A. B., Enninful, A., Benz, C., Furman, D., Beaulieu, D., Jurk, D., Thompson, E. L., Wu, F., Rodriguez, F., Barthel, G., Chen, H., Phatnani, H., Heckenbach, I., Chuang, J. H., Horrell, J., Petrescu, J., Alder, J. K., Lee, J. H., Niedernhofer, L. J., Kumar, M., Konigshoff, M., Bueno, M., Sokka, M., Scheibye-Knudsen, M., Neretti, N., Eickelberg, O., Adams, P. D., Hu, Q., Zhu, Q., Porritt, R. A., Dong, R., Peters, S., Victorelli, S., Pengo, T., Khaliullin, T., Suryadevara, V., Fu, X., Bar-Joseph, Z., Ji, Z., and Passos, J. F. (2023) Spatial mapping of cellular senescence: emerging challenges and opportunities, *Nat. Aging*, **3**, 776-790, https://doi.org/10.1038/s43587-023-00446-6.

169. Rutledge, J., Oh, H., and Wyss-Coray, T. (2022) Measuring biological age using omics data, *Nat. Rev. Genet.*, **23**, 715-727, https://doi.org/10.1038/s41576-022-00511-7.

170. Campisi, J., Kapahi, P., Lithgow, G. J., Melov, S., Newman, J. C., and Verdin, E. (2019) From discoveries in ageing research to therapeutics for healthy ageing, *Nature*, **571**, 183-192, https://doi.org/10.1038/s41586-019-1365-2.