RETHINKING THE EVOLUTIONARY ORIGIN, FUNCTION, AND TREATMENT OF CANCER

Review

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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.

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

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In memory of V.P. Skulachev

INTRODUCTION

The recent publication of "Why do cancer patients die?" [1] opens a new section "Roadmap Articles", in which the editors of *Nature Reviews Cancer* plan to publish articles that discover new approaches in cancer research and treatment [2]. The authors of the paper state that the immediate causes of death of a cancer patient remain poorly understood, and this hinders the development of new methods of treatment. It is assumed that the relevant experiments will contribute to the progress of fundamental oncology and improve clinical practice.

The same question ("What causes a cancer patient to die?") was posed 10 years earlier as an invitation to discuss the problems of tumor-organism relationships not only from the utilitarian-medical but also from the biological point of view [3]. Indeed, understanding the mechanism of death can open many opportunities for cancer treatment by blocking the various stages of this process, whereas ignorance of this mechanism condemns the physician to the only possible treatment strategy - physical destruction of the cancer cell. It is this approach that is implemented today, however complex, difficult and painful it may be. The focus of the oncological "mainstream" on intracellular processes [4], driven by the hope to find deeply hidden vulnerabilities of the cancer cell, constantly multiplies the number of its hallmarks [5-8], but there are no attempts to link them to clinical manifestations of the disease, such as weakness and weight loss, chronic inflammation, anorexia, cachexia, anemia, coagulopathy, nontosis, and multiple organ failure [9-18]. Today, as 20 years ago, "cancer research tends to focus on individual cellular mechanisms, virtually ignoring everything that happens in the body as a whole" [19]. As a result, despite many remarkable advances in basic oncology, there is a growing perception that cancer research is on the cusp of a paradigm shift [20]: practical advances remain limited, the cost of individualized therapy is unacceptably high, and the main hope remains in the art of the surgeon.

The discrepancy between the advances in basic and practical oncology appears to be, at least in part, a consequence of the triumph of a reductionist approach at the expense of holism [21]. (This conflict, as in the ancient Indian parable of the blind sages groping the elephant, is that a deep dive into details can lead the researcher away from understanding the object as a whole.) The holistic approach uses an evolutionary perspective when studying tumor-organism relationships [22]. According to the conventional viewpoint, cancer is a consequence of imperfect evolution and the result of random mutations that lead to the disruption of intercellular cooperation; cancer cells are "cheaters" that have returned to their original single-cell lifestyle [23, 24]. According to the mechanism of Darwinian evolution, they selfishly replicate, compete for survival, spread throughout

the organism, and achieve reproductive success at its expense [25-27].

Contrary to conventional wisdom, two articles have revealed to the oncological community an "elephant" - cancer as a special organ [28, 29]. Indeed, a tumor meets the formal definition of an organ as "an anatomically discrete set of tissues designed to perform specific functions" [28], and has the appropriate attributes - a complex and hierarchical structure [28], and has the appropriate attributes - a complex hierarchical structure, often mimicking the structure of normal tissue [30], the presence of stem and differentiated cells, certain stages of development and integration with body systems. Cancer is evolutionarily conservative: having appeared, apparently, simultaneously with multicellular organisms about a billion years ago, it affects most animal species [24, 27, 31].

The concept of "cancer as an organ" means a radical departure from conventional wisdom. However, although this term has entered the scientific community (the recognition that the complexity of a cancerous tumor may exceed the complexity of normal tissues is indicative [6]), the paradigm shift that has occurred has remained virtually unnoticed. The reason, apparently, is that the first decisive step (recognition of the fundamentally different nature of this phenomenon than previously thought) was not followed by the second, necessary and obvious one - discussion of the function that gave rise to this organ (it is impossible to study an organ in isolation from its function and outside the evolutionary perspective). This paper attempts to fill this gap: hereditary cancer is considered as a mechanism of purifying selection of the gene pool, sporadic cancer as a by-product of hereditary cancer, and the malignancy of the cancer cell as its main distinguishing property. It is suggested that neutralization of the cancer interactome may be an alternative treatment strategy.

EVOLUTIONARY ORIGIN OF CANCER

Early suggestions that cancer serves a purifying selection function [22, 32-35] failed to gain traction because most individuals that cancer kills are in postreproductive age [36]. However, the concept of "cancer as an organ" revives the debate because every organ has an evolutionary basis for its existence.

There are two types of cancer (hereditary and sporadic), and only the former is capable of negative selection. Hereditary cancer results from a germinal mutation in one of several dozen critical genes [34, 37] involved in DNA repair, cell cycle regulation, and apoptosis [38]. A germinal driver mutation, present in every cell of an organism (including its germ cells), creates a high risk of cancer development in its carrier for two reasons: firstly, the path of cellular transformation is shortened and, secondly, the future cancer cell is initially located in a genetically unfavorable

microenvironment (the situation of a "criminal 'seed' in a criminogenic 'soil'" [39]). Thus, the germinal driver mutation creates a double danger: for the organism (high risk of highly penetrant cancer at an early age) and for the species (high probability of transmission to offspring). However, the realization of the first possibility prevents the second (as Steve Sommer puts it, "cancer kills the individual and saves the species" [33]). Hereditary cancer syndromes with Mendelian dominant inheritance sharply reduce the reproductive success of offspring [40] and purify the gene pool from mutant alleles (frequency of predisposing alleles in the population< 1%) [41, 42].

Hereditary cancer is relatively rare [43-51], accounting for only ~1% of cancer incidence. The question arises how to explain the huge quantitative predominance of sporadic cancer, which is caused by somatic (not inherited) mutations, evolves over decades, and affects mainly people of postreproductive age. Indeed, why kill old people who do not participate in evolution? Perhaps the answer 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], we can assume that cancer is present in old ages "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 huge quantitative prevalence in *Homo sapiens* is a payment for artificially created comfortable life (with all its excesses and bad habits), for constantly increasing (~2.5 years per decade) life expectancy due to changes in hygiene, health care, and nutrition [40], as well as for the aging-induced decrease in transformational resistance of stem cells [54]. In countries with an average life expectancy of 75-80 years, the risk of getting cancer is now ~50%, and at a life expectancy of 120 years, it is projected to be almost 90% in men and more than 70% in women [55]. The high incidence of cancer is probably a peculiarity of *H. sapiens* - this far from typical representative of the animal world. Most other mammalian species have much lower incidence rates [27, 56].

To illustrate the difference between hereditary and sporadic forms, consider the analogy of cancer to the self-destruct mechanism built into a rocket; hidden under normal conditions, it only reveals itself in the event of an accident. This mechanism may work properly, preventing catastrophic consequences in the rare event of a missile failure (hereditary cancer), but it can fail as a result of aging and deterioration of parts during storage. The longer the storage, the more frequent the failures (sporadic cancer). While in the first case the process is initiated by one of a small number of defined deviations from the standard procedure (and thus realized by a few well-defined scenarios), in the second case it is initiated by a combination of many random defects accumulated over a long period of time (and thus realization is possible in many variants). This analogy can explain the differences in the mutational landscapes of hereditary and sporadic forms of cancer [57-59], as well as their clinical, morphological, and molecular differences.

The widespread use of next-generation sequencing (NGS) for hereditary testing has made it possible to experimentally investigate genotype-phenotype correlations in cancer patients [60]. Although the phenomenon of purifying selection in hereditary cancer seems unquestionable, recent studies have questioned its efficacy. It turned out that germline pathogenic variants (GPV) predisposing to highly penetrant cancers are more common than expected [51, 61, 62]. More than a quarter of cancers in carriers of such GPVs did not have specific features associated with the germline allele [58]. This suggested that the tumors developed independently of it and, therefore, GPVs are less penetrant than previously thought [63].

Several considerations can be made in connection with these data. First, the determination of the status of inherited mutations is complicated by the unexpectedly wide spread of such phenomena as postzygotic mosaicism, aberrant clonal expansion, and clonal hematopoiesis [47, 64-76], which sometimes leads to misclassification. Second, when studying cancer as a biological phenomenon, *H. sapiens* can hardly be considered as a representative experimental model. In the animal world, cancer has a significant impact on the competitive abilities of individuals, their susceptibility to pathogens, vulnerability to predators, and ability to disperse [31]. Habitat conditions, in turn, influence the pathogenesis of the disease. Thousands of years of civilization have brought about such drastic changes in human lifestyle (hygiene, health care, nutrition) and environment that they may have significantly reduced the selective pressure of hereditary cancer. Third, a recent study of the evolutionary impact of childhood cancer on the human gene pool found that pediatric cancer predisposition syndrome genes (pediatric cancer predisposition syndrome genes) are under strong selective pressure. The authors summarize that hereditary childhood cancer is a natural selection process that significantly affects the modern gene pool [77].

The hypothesis that "cancer kills the individual and saves the species" [33] leads to a counterintuitive view of cancer as an altruistic phenomenon [33], leads to a counterintuitive view of cancer as an altruistic phenomenon. The basis of biological evolution, according to Darwin, is individual selection (i.e., selfishness is its driving force). However, "perhaps the most remarkable property of evolution is its ability to engender cooperation in a competitive world" [78]. The contradiction between the tenets of Darwin's theory and the abundance of examples of cooperation and altruism in the wild was resolved a century later in the theories of inclusive adaptation, kin selection [79, 80], and the "selfish gene" [81]. Although theoretical debates continue to this day (see Nowak et al. [82], Abbot et al. [83], Kay et al. [84] and Efferson et al. [85]), the existence of cooperation and altruism in biological communities is beyond doubt.

Altruism is most actively discussed in connection with the phenomenon of aging, starting with Weisman's early ideas about programmed aging and ending with the concept of programmed and altruistic aging put forward in the work of Skulachev et al [86]. Within the framework of the

latter, the idea of *phenoptosis* (programmed death of an organism) is developed. By analogy with the cells of multicellular organisms possessing a mechanism of self-destruction (apoptosis) [87], it is assumed that "complex biological systems are equipped with programs that eliminate those elements of the system that have become dangerous or unnecessary for the system as a whole" [88]. [88]. It can be assumed that cancer is a special case of phenoptosis. At the level of a multicellular organism the spread of dangerous defects is counteracted by apoptosis, while at the level of a population this work is performed by cancer. It seems likely 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 in the cell and that cancer is as irreversible as the mutations themselves. While mutations do indeed precede cancer in the vast majority of cases, they are not absolutely required for carcinogenesis. Tumors with few or no mutations are known [89], and cancer reversion can occur despite their presence [90, 91]. Epigenetic reprogramming itself can stimulate tumor growth [92], in particular, inhibition of Polycomb group proteins synthesis causes irreversible tumor growth in fruit flies [93]. These facts are consistent with the idea of cancer as an alteration of normal cell differentiation [94]. In light of Waddington's concept of epigenetic landscapes, driver mutations induce epigenetic reprogramming leading to a critical transition from the fixed state of a normal cell to the fixed state of a cancer cell [91]. This point of view is supported by genetic analysis of several types of cancer (breast, colon, pancreas, glioblastoma), which showed that driver mutations, which differ significantly in these species, nevertheless damage the same signaling pathways [95].

These data make us reconsider the role of driver mutations in carcinogenesis. They may not be the driving force of the stochastic process of carcinogenesis, but rather the triggers of a pre-existing evolutionarily conserved epigenetic program. The apparent similarities between embryogenesis and tumorogenesis suggest oncofetal reprogramming that allows cancer cells to evade the immune response and facilitates their proliferation and metastasis [96]. The concept of driver mutations as a trigger of epigenetic transdifferentiation can reconcile conflicting theories: SMT (Somatic Mutation Theory) [97], which considers cancer as a cellular pathology, and TOFT (Tissue Organization Field Theory) [98, 99], which considers cancer a tissue pathology caused by developmental defects.

CANCER AS PROGRAMMED DEATH

Cancer as an organ must have a function, and it is obvious - it is a killer function, realized in stages and having the features of programmed death of the organism [35, 100]. The term "cancer transformation" denotes a more profound change than just the acquisition by a cell of a number of phenotypic features, such as unregulated division, namely a radical change in its social behavior: a "creator cell" becomes a "destroyer cell". While a normal cell maintains the homeostasis of the organism, a cancer cell, like a "zombie", subordinates the host's metabolism to its needs [101], builds a "niche" [102, 103], provides itself with blood supply [104], energy [105] and innervation [8, 106, 107], forms a microenvironment and premetastatic niches [108-112], colonizes the organism 113] and, finally, kills it and itself.

The death of a cancer patient is perceived as something so obvious, self-evident and intrinsic to cancer that its killer function is not explicitly articulated, not given the attention it deserves, and not on the list of its distinguishing features. The traditional view that cancer mortality is a consequence of metastasis identifies metastasis with *malignancy*, that is, the ability of a cancer cell to kill the organism (the term "*malignancy*" is used here to distinguish it from "*malignancy*," which refers to cancer pathology in general). It is obvious, however, that metastasis (spreading through the body) and malignancy are properties of a cancer cell that, although closely related, are essentially different. In this respect, the fact that the *NALCN* gene regulates both metastasis of cancer cells and dissemination of normal cells without metastasis is significant [114]. There is much evidence that systemic effects rather than metastasis *per se* are the cause of most cancer deaths [1, 29, 115].

Malignancy seems to be the property of the cancer cell that "is still waiting to be recognized" [116]: it is the property that forms the functional relationship between the tumor and the organism, while all other properties play only a supporting role. [116]: it is the property that forms the functional relationship between the tumor and the organism, while all other properties seem to play only an auxiliary role. Malignancy is realized through a diverse toolbox including secreted factors, extracellular vesicles, circulating nucleic acids and neurogenic factors [8, 101, 117-133]. This arsenal, which can be labeled as the cancer interactome, is capable of affecting distant tissues, causing various paraneoplastic syndromes [9-13, 101, 134-136]. The interactomes of normal and cancer cells possessing the same genome should be essentially the same. Apparently, the differences are only in "targeting": those means, which a normal cell uses to maintain the homeostasis of the organism, a cancer cell directs to its destruction, using inadequately in time and/or place, in unacceptable concentrations and/or combinations. One such "dual purpose" agent

is the senescence-associated secretory phenotype (senescence-associated secretory phenotype, SASP), which serves as an antitumor defense mechanism in normal aging but a pro-tumorigenic factor in cells induced by genotoxic stress [121, 137, 138]. Perhaps the most significant manifestation of cancer cell malignancy is chronic inflammation, which often precedes and always accompanies malignant growth [96, 139-145]. As a fundamental defense mechanism designed to fight infections and promote wound healing, "it is antagonistic to the body's homeostatic mechanisms, which explains the inevitable impairment of many functions" [146]. Recently, the fusion of extracellular vesicles with target cells has been shown to be a trigger of systemic inflammation [147]. One consequence of inflammation is also neutrophil extracellular traps (NETs), a defense mechanism designed to capture and neutralize microbes but capable of causing multi-organ failure when pathologically activated chronically [17, 148-152]. Cachexia is also associated with the inflammatory process [153-155]. Recently, the involvement of the peripheral and central nervous system in the cancer process has been revealed [8, 156-158].

NEUTRALIZATION OF THE CANCEROUS INTERACTOME AS A TREATMENT STRATEGY

If we consider cancer as a special organ, its development as a series of predetermined events, and its lethal outcome as a result of its inherent specific function, then understanding the mechanism of the latter is a prerequisite for successful fight against this evil. The generally accepted statement "cancer is not one, but many different diseases", stating the diversity of its manifestations, reflects the clinical point of view. However, the experimenter sees in this diversity a single, albeit multivariant, pathogenetic mechanism.

Progress in the war against cancer is unsatisfactory for two main reasons. First, cancer cells quickly learn to avoid the means of defeat and, after the first, often very significant losses, regain their former positions and go on the offensive [159]. Second, the profound affinity between cancer and normal cells makes chemotherapy a form of "friendly fire" with concomitant, sometimes severe, losses. This situation makes it necessary to consider alternatives to the current treatment strategy aimed at killing cancer cells, such as adaptive therapy [160, 161], the "tolerant defense" strategy [162, 163], cancer reversion strategy [91], neutralization strategy based on "antidotes" instead of "poisons" [164]. In the latter case, it is supposed to reorient the means of fighting an organ to its function, i.e. to the cancerous interactome. This is precisely the strategy of "neutralization" applied by man in the fight against his external enemies (poisonous animals): effective and relatively harmless specific antidotes are used instead of hopeless and ruinous

attempts to completely destroy the animals themselves. Such a treatment strategy may have several advantages over the current one: (1) being less toxic; (2) having lower cost (provided that different cancers have similar harmful interactome); and (3) being suitable for chemoprevention, which uses drugs to block the early stages of carcinogenesis [165]. Known examples of neutralizing strategies today are the use of non-steroidal anti-inflammatory drugs (NSAIDs) to relieve symptoms and improve the well-being of cancer patients [166] and the injection of DNAase I into experimental animals to inhibit nontumor associated metastasis [148].

To obtain an effective antidote, it is necessary to know the mechanism of the deleterious effect. In the case of cancer, this means a thorough study of the tumor impact on distant tissues mediated by the interactome. It is necessary to find out the degree of variability and specificity of both the cancer interactome itself and its tissue and metabolic targets. In this context, studies of the aging process, the object of which is the whole organism, are indicative. At the same time, the whole range of high-throughput "omics" technologies was used to study molecular processes in various 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 obtained knowledge has led to significant practical results [170], a holistic approach to the malignant tumor-affected organism will make it possible to find ways to avoid its devastating effects.

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CONFLICT OF INTERESTS

The author declares no conflicts of interest.

ETHICS DECLARATION

The article does not contain a description of research conducted by the author with human participants or using animals as subjects.

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.
2. Editorial (2024) The road less traveled, *Nat. Rev. Cancer*, **24**, 515.
3. Lichtenstein, A. V. (2014) Cancer research: a hurdle race, *Biochemistry (Moscow)*, **79**,

385-390.

4. Laplane, L., and Maley, C. C. (2024) The evolutionary theory of cancer: challenges and potential solutions, *Nat. Rev. Cancer*, **24**, 718-733.
5. Hanahan, D., and Weinberg, R. A. (2000) The hallmarks of cancer, *Cell***, 100**, 57-70.
6. Hanahan, D., and Weinberg, R. (2011) Hallmarks of cancer: the next generation, *Cell*, **144**, 646-674.
7. Hanahan, D. (2022) Hallmarks of cancer: new dimensions, *Cancer Discov.*, **12**, 31-46.
8. Hanahan, D., and Monje, M. (2023) Cancer hallmarks intersect with neuroscience in the tumor microenvironment, *Cancer Cell*, **41**, 573-580.
9. Tisdale, M. J. (2002) Cachexia in cancer patients, *Nat. Rev. Cancer*, **2**, 862-871.
10. Finora, K. (2003) Common paraneoplastic syndromes, *Clin. Tech. Small Anim. Pract*, **18**, 123-126.
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.
12. Mazzone, P. J., and Arroliga, A. C. (2003) Endocrine paraneoplastic syndromes in lung cancer, *Curr. Opin. Pulm. Med.*, **9**, 313-320.
13. Posner, J. B. (2003) Immunology of paraneoplastic syndromes: overview, *Ann. N. Y. Acad. Sci.*, **998**, 178-186.
14. Spivak, J. L. (2005) The anaemia of cancer: death by a thousand cuts, *Nat. Rev. Cancer*, **5**, 543-555.
15. Rak, J., Klement, P., and Yu, J. (2006) Genetic determinants of cancer coagulopathy, angiogenesis and disease progression, *Vnitr. Lek.*, **52 Suppl 1**, 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.
17. Jorch, S. K., and Kubes, P. (2017) An emerging role for neutrophil extracellular traps in noninfectious disease, *Nat. Med.*, **23**, 279-287.
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.
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.

21. Yuzhalin, A. E. (2024) Redefining cancer research for therapeutic breakthroughs, *Br. J. Cancer*, **130**, 1078-1082.
22. Lichtenstein, A. V. (2005) On the evolutionary origin of cancer, *Cancer Cell Int.*, **5**, 5.
23. Bozic, I., and Nowak, M. A. (2013) Unwanted evolution, *Science*, **342**, 938-939.
24. Greaves, M. (2007) Darwinian medicine: a case for cancer, *Nat. Rev. Cancer*, **7**, 213-221.
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.
26. Aktipis, C. A., and Nesse, R. M. (2013) Evolutionary foundations for cancer biology, *Evol. Appl*., **6**, 144-159.
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**, 1-21.
28. Bissell, M. J., and Radisky, D. (2001) Putting tumors in context, *Nat. Rev. Cancer*, **1**, 46-54.
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.
30. Perez-Losada, J., and Balmain, A. (2003) Stem-cell hierarchy in skin cancer, *Nat. Rev. Cancer*, 3, 434-443.
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.
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.
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.
35. Lichtenstein, A. V. (2010) Cancer: evolutionary, genetic and epigenetic aspects, *Clin Epigenetics*, **1**, 85-100.
36. Leroi, A. M., Koufopanou, V., and Burt, A. (2003) Opinion: cancer selection, *Nat. Rev. Cancer*, **3**, 226-231.
37. Rahman, N. (2014) Realizing the promise of cancer predisposition genes, *Nature*, **505**, 302-308.

38. Frank, S. A. (2004) Genetic predisposition to cancer - insights from population genetics, *Nat. Rev. Genet*., **5**, 764-772.
39. Lichtenstein, A. V. (2018) Genetic mosaicism and cancer: cause and effect, *Cancer Res.*, **78**, 1375-1378.
40. Byars, S. G., and Voskarides, K. (2020) Antagonistic pleiotropy in human disease, *J. Mol. Evol*., **88**, 12-25.
41. Ponder, B. A. (2001) Cancer genetics, *Nature*, **411**, 336-341.
42. Yang, X., Kar, S., Antoniou, A. C., and Pharoah, P. D. P. (2023) Polygenic scores in cancer, *Nat. Rev. Cancer*, **23**, 619-630.
43. Marsh, D. J., and Zori, R. T. (2002) Genetic insights into familial cancers - updates and recent discoveries, *Cancer Lett*., **181**, 125-164.
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.
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.
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.
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.
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.
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.
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.
52. Williams, G. C. (1957) Pleiotropy, natural selection, and the evolution of senescence,

Evolution, **11**, 398-411.

53. Austad, S. N., and Hoffman, J. M. (2018) Is antagonistic pleiotropy ubiquitous in aging biology? *Evol. Med. Public Health*, **2018**, 287-294.
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.
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.
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.
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.
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., et al. (2021) The context-specific role of germline pathogenicity in tumorigenesis, *Nat. Genet*., **53**, 1577-1585.
59. Dolgin, E. (2020) Cancer genome complexity made simple, *Cancer Discov*.**, 10**, 480.
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.
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.
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.
63. Torrezan, G. T. (2023) Untangling the mechanisms of cancer predisposition, *Nat. Rev. Cancer*, **23**, 429-429.

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. et al (2012) *De novo* germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes, *Nat. Genet*., **44**, 934-940.

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.

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.

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 germ-line testing results, *Genet. Med*., **20**, 809-816.

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 have had hereditary pan-cancer panel testing, *Cancer Genet*., **235-236**, 31-38.

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.

70. Jaiswal, S., and Ebert, B. L. (2019) Clonal hematopoiesis in human aging and disease, *Science*, **366**, eaan4673.

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.

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.

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.
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.
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 Tumor Syndrome and literature review, *Eur. J. Med. Genet.*, **65**, 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.
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.
78. Nowak, M. A. (2006) Five rules for the evolution of cooperation, *Science*, **314**, 1560-1563.
79. Hamilton, W. D. (1964) The genetic evolution of social behavior. I and II, *J. Theor. Biol.*, **7**, 1-52.
80. Maynard-Smith, J. (1964) Group selection and kin selection, *Nature*, **201**, 1145-1147.
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.
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., et al. (2011) Inclusive fitness theory and eusociality, *Nature*, **471**, E1-E4.

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.
85. Efferson, C., Bernhard, H., Fischbacher, U., and Fehr, E. (2024) Super-additive cooperation, *Nature***, 626**, 1034-1041.
86. Longo, V. D., Mitteldorf, J., and Skulachev, V. P. (2005) Programmed and altruistic aging, *Nat. Rev. Genet*., **6**, 866-872.
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.
88. Skulachev, V. P. (2001) The programmed death phenomena, aging, and the Samurai law of biology, *Exp. Gerontol*., **36**, 995-1024.
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.
90. Mintz, B., and Illmensee, K. (1975) Normal genetically mosaic mice produced from malignant teratocarcinoma cells, *Proc. Natl. Acad. Sci. USA*, **72**, 3585-3589.
91. Shin, D., and Cho, K. H. (2023) Critical transition and reversion of tumorigenesis, *Exp. Mol. Med*., **55**, 692-705.
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.
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.
94. Sporn, M. B. (1996) The war on cancer, *Lancet*, **347**, 1377-1381.
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.
96. Sharma, A., Bleriot, C., Currenti, J., and Ginhoux, F. (2022) Oncofetal reprogramming in tumor development and progression, *Nat. Rev. Cancer*, **22**, 593-602.

97. Greaves, M., and Maley, C. C. (2012) Clonal evolution in cancer, *Nature*, **481**, 306-313.
98. Sonnenschein, C., Soto, A. M., Rangarajan, A., and Kulkarni, P. (2014) Competing views on cancer, *J. Biosci.*, **39**, 281-302.
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.
100. Lichtenstein, A. (2005) Cancer as a programmed death of an organism, *Biochemistry (Moscow)*, **70**, 1055-1064.
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., et al. (2023) Tumor extracellular vesicles and particles induce liver metabolic dysfunction, *Nature***, 618**, 374-382.
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.
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.
104. Bergers, G., and Benjamin, L. E. (2003) Tumorigenesis and the angiogenic switch, *Nat. Rev. Cancer*, **3**, 401-410.
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.
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.
107. Magnon, C., and Hondermarck, H. (2023) The neural addiction of cancer, *Nat. Rev. Cancer*, **23**, 317-334.
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.
109. Kaplan, R. N., Rafii, S., and Lyden, D. (2006) Preparing the "soil": the premetastatic niche, *Cancer Res.*, **66**, 11089-11093.
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.

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.
112. Patras, L., Shaashua, L., Matei, I., and Lyden, D. (2023) Immune determinants of the pre-metastatic niche, *Cancer Cell*, **41**, 546-572.
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.
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.
115. McAllister, S. S., and Weinberg, R. A. (2010) Tumor-host interactions: a far-reaching relationship, *J. Clin. Oncol*., **28**, 4022-4028.
116. Bilder, D., Ong, K., Hsi, T. C., Adiga, K., and Kim, J. (2021) Tumor-host interactions through the lens of *Drosophila*, *Nat. Rev. Cancer*, **21**, 687-700.
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.
118. Anastasiadou, E., and Slack, F. J. (2014) Malicious exosomes, *Science*, **346**, 1459-1460.
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.
120. Balkwill, F. (2004) Cancer and the chemokine network, *Nat. Rev. Cancer*, **4**, 540-550.
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 Russian Academy of Sciences and the p53 tumor suppressor, *PLoS Biol*., **6**, 2853-2868.
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.
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.
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.

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.
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.
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.
128. Moller, A., and Lobb, R. J. (2020) The evolving translational potential of small extracellular vesicles in cancer, *Nat. Rev. Cancer*, **20**, 697-709.
129. Nikitina, I. G., Sabirova, E. Yu., Karpov, V. L., Lisitsyn, N. A., and Beresten, S. F. (2013) The role of exosomes and microvesicles in carcinogenesis, Mol. A., and Beresten, S. F. (2013) The role of exosomes and microvesicles in carcinogenesis, *Mol. Biol. (Mosk)*, **47**, 767-773.
130. Rak, J. (2013) Extracellular vesicles - biomarkers and effectors of the cellular interactome in cancer, *Front. Pharmacol*., **4**, 1-14.
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.
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.
133. Rak, J. (2015) Cancer: organ-seeking vesicles, *Nature*, **527**, 312-314.
134. Darnell, R. B., and Posner, J. B. (2003) Paraneoplastic syndromes involving the nervous system, *N. Engl. J. Med.*, **349**, 1543-1554.
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.
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.
137. Campisi, J. (2013) Aging, cellular senescence, and cancer, *Annu. Rev. Physiol*., **75**, 685-

705.

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.
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.
140. Balkwill, F., and Mantovani, A. (2001) Inflammation and cancer: back to Virchow? *Lancet*, **357**, 539-545.
141. Coussens, L. M., and Werb, Z. (2002) Inflammation and cancer, *Nature*, **420**, 860-867.
142. Mantovani, A., Allavena, P., Sica, A., and Balkwill, F. (2008) Cancer-related inflammation, *Nature*, **454**, 436-444.
143. Coussens, L. M., Zitvogel, L., and Palucka, A. K. (2013) Neutralizing tumor-promoting chronic inflammation: a magic bullet? *Science*, **339**, 286-291.
144. Grivennikov, S. I., Greten, F. R., and Karin, M. (2010) Immunity, inflammation, and cancer, *Cell*, **140**, 883-899.
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.
146. Okin, D., and Medzhitov, R. (2012) Evolution of inflammatory diseases, *Curr. Biol*., **22**, R733-R740.
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.
148. Hawes, M. C., Wen, F., and Elquza, E. (2015) Extracellular DNA: a bridge to cancer, *Cancer Res.*, **75**, 4260-4264.
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.
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.
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.

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.
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.
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.
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.
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.
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.
158. Zahalka, A. H., and Frenette, P. S. (2020) Nerves in cancer, *Nat. Rev. Cancer*, **20**, 143-157.
159. Hanahan, D. (2014) Rethinking the war on cancer, *Lancet*, **383**, 558-563.
160. Gatenby, R. A., Silva, A. S., Gillies, R. J., and Frieden, B. R. (2009) Adaptive therapy, *Cancer Res.*, **69**, 4894-4903.
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.
162. Medzhitov, R., Schneider, D. S., and Soares, M. P. (2012) Disease tolerance as a defense strategy, *Science*, **335**, 936-941.
163. Rao, S., and Ayres, J. (2017) Resistance and tolerance defenses in cancer: Lessons from infectious diseases, *Semin. Immunol.*, **32**, 61.
164. Lichtenstein, A. V. (2018) Strategies of the war on cancer: to kill or to neutralize? *Front. Oncol.*, **8**, 667.
165. Sporn, M. B., and Suh, N. (2002) Chemoprevention: an essential approach to controlling cancer, *Nat. Rev. Cancer*, **2**, 537-543.
166. Roxburgh, C. S. D., and McMillan, D. C. (2014) Cancer and systemic inflammation: treat the tumor and treat the host, *Br. J. Cancer*, **110**, 1409-1412.

167. Valdes, A. M., Glass, D., and Spector, T. D. (2013) Omics technologies and the study of human aging, *Nat. Rev. Genet*., **14**, 601-607.

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., et al. (2023) Spatial mapping of cellular senescence: emerging challenges and opportunities, *Nat. Aging*, **3**, 776-790.

169. Rutledge, J., Oh, H., and Wyss-Coray, T. (2022) Measuring biological age using omics data, *Nat. Rev. Genet*., **23**, 715-727.

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.