Hypothesis of the Basic Biological Sense of Cancer Revisited - A Putative Explanation of Peto's Paradox

Oscar D Bustuoabad and Raúl A Ruggiero*

Laboratory of Experimental Oncology, IMEX-Conicet, Academia Nacional de Medicina de Buenos Aires, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina

*Corresponding author: Raúl A. Ruggiero
Email: ruloruggiero@yahoo.com.ar

Abstract

The conventional interpretation of cancer, summarized in the *unified genetic theory of carcinogenesis*, assumes that *the malignant cell is the anatomical and physiological unit of cancer.* This assumption means that any evolutionary increase in the number of cells (and thus body size) should lead to a higher tumor incidence since the population at risk is higher. However, the available data fail to support this prediction: most animals, in particular most mammals, exhibiting wide differences in body size and lifespan, from the mouse to the blue whale, display a roughly similar tumor incidence. This unexpected lack of correlation between body size, lifespan and cancer is usually called Peto's paradox and it has intrigued theoretical oncologists for decades.

In this essay, we attempt to offer a putative explanation of this paradox based on the notion that *the unit at risk of carcinogenesis is actually the tissue or organ rather than the individual cell*. In turn, this notion is based on a different interpretation of neoplastic diseases that we proposed some years ago and that has been called the *hypothesis of the biological sense of cancer.*

This hypothesis was based on the observation that throughout the animal kingdom, cancer seems to arise only in organs and tissues (or parts of them) that have experienced a significant decrease in the regenerative ability, and this would occur when a critical proportion of their cells have partially or wholly lost that capacity. In such a case, if an organism or an organ were x times larger than another one, the probability that its regenerative capacity is critically diminished would be x times lower, because an x times greater number of cells would have to be affected to depress that capacity. This lower probability would balance the proportionally higher number of their cells that could be transformed and this would explain why the blue whale displays no greater risk of developing cancer than the mouse *by unit of time*. However, since big animals tend to live y times longer than small ones, it remains to explain why both animals may display a similar tumor incidence *by lifespan*. The concept of mass-specific basal metabolic rate (msBMR) can account for this problem since msBMR diminishes with body weight as much as lifespan increases meaning that the time for individual cells to get both the natural decline in regenerative ability and potential neoplastic mutations should be, in the big animal, y times slower than in the small one. This could explain why the tumor incidence in blue whales along their long lifespan may be not higher than that observed in mice along their short life.

A "unified genetic theory of carcinogenesis"

Since 1863, when Virchow extended his aphorism *omnis cellula e cellula* to include cancer cells, many researchers have proposed different theories aimed to understand the nature of cancer and to answer the question of how tumors appear to begin with [1-3]. Since the late1970, different alterations in cellular genes as well as in several intracellular transducing signaling pathways have been identified in cancer cells, and on this basis a unified genetic theory of carcinogenesis has been advanced [4-9].

This "theory" states that cancer starts and ends with the malignant cell, in which genetic changes lead to constitutive activation of some genes (oncogenes) and/or inactivation of others (anti-oncogenes or tumor suppressor genes) allowing cells to evade the mechanisms controlling their proliferation. These genetic changes would define the molecular and cellular attributes of the cancer cell, which, in turn, should be the target of specific therapies against cancer. This theory has the particular merit of unifying through an immediate common pathway the numerous different mediators that cause cancer, such as chemicals, radiation, viruses, etc. However, it has some theoretical difficulties, which have been addressed by certain authors [10-13] who have also emphasized that – apart from some particular advances in targeted molecular therapies against certain tumors [14] - cancer remains a major cause of morbidity and mortality, despite the explosive development of our knowledge about the molecular mechanisms associated with the control of cell cycle and survival [15-17]. In fact, if all cells in an organism have roughly equal possibilities of oncogene activation and/or tumor-suppressor gene inactivation, then, all else being equal, the number of cells susceptible to transformation should scale with body size, implying that very large animals such as rhinoceros, elephants and whales should be much more prone to cancer than very small ones, such as mice, since the cell population at risk is greater by several orders of magnitude. However, available data fail to support this prediction [18-20]. The unexpected lack of correlation between body size and cancer risk across species has been dubbed Peto's paradox, since the statistical epidemiologist, Richard Peto, made this observation in 1977 [21]. Of course, this and other theoretical difficulties and the persistent failure in treating cancer do not necessarily imply that the "unified genetic theory of carcinogenesis" is incorrect. However, they encourage us to consider other possibilities.

The hypothesis of the basic biological sense of cancer

Some years ago, in an attempt to explore other theoretical approaches to cancer, we proposed [22, 23], - on the basis of ideas advanced by Prehn, Zajicek, Bissell, Sonnenschein and Soto among others [24-28] – the hypothesis of the biological sense of cancer.

This hypothesis is based on the observation that throughout the animal kingdom, cancer is rarely – if ever – induced in organs or tissues displaying an efficient reparative or regenerative mechanism, "efficient" meaning the ability of organs and tissues to regenerate numerically and functionally. In effect, when these mechanisms remain fairly efficient throughout life – even under the action of putative noxious agents – as they do in animals displaying strong regenerative ability - "strong" meaning the ability

to regenerate complex structures such as a whole limb or large regions of the body - cancer never (or almost never) occurs [29-41] (**FIGURE 1**).

On the other hand, when the reparative mechanisms remain efficient only during youth – and even during youth, some noxious agents can deplete them – as they do in animals displaying weak regenerative ability - "weak" meaning the ability to repair or regenerate only relatively simple structures, as in compensatory hyperplasia of the liver, skin regeneration, etc. - cancer occurs mainly in aging individuals and also in injured organs from young individuals that may have experienced a significant decline of their regenerative ability because of the action of those noxious agents [22-24, 30, 33, 34, 42-61] (**FIGURE 1**).

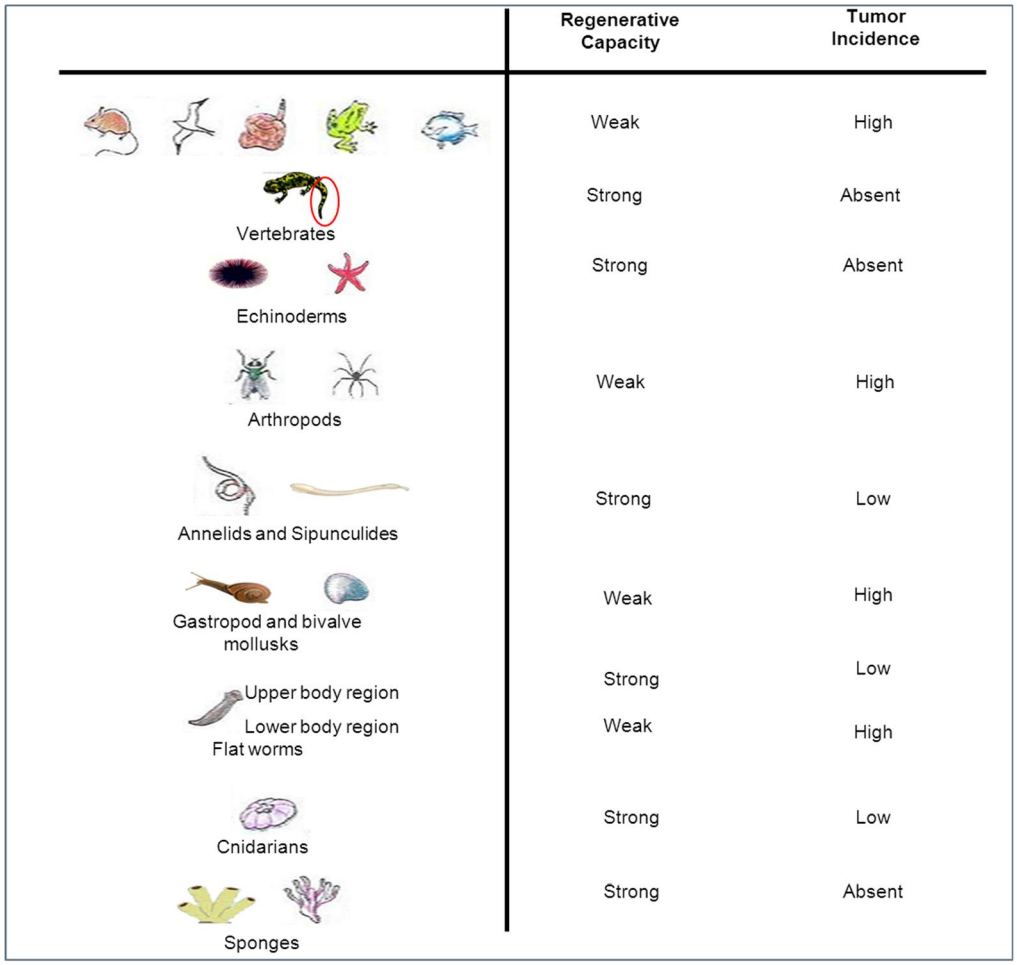

FIGURE 1: General relationship between regenerative capacity and tumor incidence among the major metazoa groups.

According to this interpretation, the origin of cancer could be envisaged as follows: when an organism has efficient regenerative mechanisms, cancer would not be produced. However, when an organism becomes aged - or is affected by noxious agents - and its regenerative ability declines progressively [58, 62], any injury causing loss of cells or diminished cellular function cannot be adequately compensated by cellular division. In consequence, the original size and function of the organ cannot be restored. We suggest that this situation induces a "**crisis**", which, through putative

danger signals resulting from retardation of tissue repair and functional compromise, could create an environment capable of promoting some degree of variability in the remaining cells of the injured organ that do not exhibit efficient reparative abilities. The outcome of this situation would be the emergence of some genetically and/or epigenetically modified cell variants. Most of these would still lack the ability to respond adequately to the organ demand, but sooner or later a variant bearing that mitotic ability would emerge by chance. This new variant would begin to divide; and if it were poorly functional or non-functional, the organ would be numerically but not functionally restored. In consequence, it would not score the regeneration as effective and it would continue to send mitotic signals to restore the lost or diminished organ function. As a result, the new variant would grow over and over and the outcome would be a tumor.

Injury, development and cancer

Many authors have highlighted the critical importance of injury in the development of cancer [60, 63-71], and the idea that cancer actually behaves as a wound healing process has been suggested by Dvorak [72-74]. On the other hand, cellular heterogeneity, and a genomic instability phase during stages of high-grade dysplasia prior to the acquisition of a frankly malignant phenotype, are two well-documented (though so far unexplained) phenomena [62, 75-77]. Similarly, well-documented are the picture of a tumor arising in a tissue surrounded by "normal" arrested and/or senescent cells, and the existence of factors involved in organ and tissue regeneration or produced directly by senescent cells that alter the local tissue microenvironment and that contribute, enhance or are necessary for tumor growth [26, 65, 78-80]. Furthermore, the induction of cell variability in aged organs associated with both an increased cell-to-cell transcriptional variability and an increased rate of mutations has also been recently demonstrated. In effect, Martínez-Jiménez et al [81] explored how natural aging impacts transcriptional dynamics using single cell RNA sequencing of un-stimulated and stimulated naïve and effector memory CD4+T cells from young and old mice from two divergent species. They demonstrated that in young animals, immunological activation drives a conserved transcriptomic switch characterized by a strong up regulation of a core activation program coupled with a decrease in cellular variability. On the other hand, aging perturbed the activation of this core program and increased the cell-to-cell transcriptional heterogeneity in both divergent species [81]. In the same way, Ban and Kai suggested that replicative stress after irradiation accelerates the ageing of hematopoietic stem cells and that the ageing-related decline of mechanisms of DNA repair could increase the rates of spontaneous mutations [82].

In summary, the hypothesis of the biological sense of cancer does not consider cancer an autonomous entity disobeying the mechanisms controlling cell proliferation, but one dependent on a reparative signal originating in the particular environment of an injured organ or tissue with diminished reparative ability. According to this interpretation, cancer would have a profound biological sense: it would eventually be the ultimate attempt to restore organ functions and structures that have been lost or altered by aging or noxious environmental agents. However, unlike normal structures, cancer would have no physiological value, because the usually poor or non-functional nature of its cells would make their reparative task unattainable.

Dependency of cancer on reparative processes

Our suggestion that a tumor cell is not autonomous, but dependent on a reparative or regenerative signal originating in an "aged" organ or tissue seems heretical, because it contradicts the classical definition of Ewing ("A neoplasm is an autonomous, or relatively autonomous, growth of tissue"), which has guided cancer research for the last 70 or more years [83]. However, closer examination of Ewing's proposition reveals that it is a postulate rather than a true definition. First, pathologists do not use it as an operational tool to diagnose the presence of a tumor; in fact, "the means to diagnose cancer have not changed that much since"... the 19th century, "when pathologists began describing the histological pattern of tumors using the light microscope" [84]. Second, if nobody knows exactly what the mechanisms control normal cell proliferation [84], how can anyone be absolutely sure that cancer cells are disobeying those mechanisms? Many years ago, Dr. Joseph Aub suggested that the "ugly word autonomy" be dropped, because, while one can prove dependency, one can never be certain of autonomy [85].

Peto's paradox: the riddle of the blue whale and the mouse

The unified genetic theory of carcinogenesis postulates the idea that *the malignant cell is the physiological and anatomical unit of cancer disease.* Implicit in this contention is the assumption that the probability of origin of an aberrant, neoplastic cell lineage is the same per unit of cell population, regardless of species or cell type concerned.

However, this assumption evokes one of the most intriguing riddles in cancer research, which remains unsolved. This riddle, stated by Dawe [31] and later by Peto [21, 86] many years ago, asks: "Why don't extremely large animals develop neoplasms with a much higher incidence than very small ones since the cell population at risk is greater by several orders of magnitude?" As an extreme example, let us consider the blue whale and the mouse. "If one takes the weight of the mouse as 30 g and that of the blue whale as 100 tons the whale is equivalent to 3,333,333 mice. Then, if one accounts for differences of lifespan (80 years for the blue whale, 2 years for the mouse, the ratio of weight-year units per whale to weight-year units per mouse is about 133,333,333" [31]. We should therefore expect the blue whale to develop neoplasms about 3×10^6 times and 130×10^6 times more often than the mouse per unit time and per lifespan, respectively. Since about 25% [range 9.5-40%] of wild mice kept under laboratory observation develop spontaneous malignant neoplasms during their lives [87-89], we should expect each blue whale to develop about 33×10^6 malignant neoplasms per lifespan (**FIGURE 2**). It is clear that these expectations do not match reality: the incidence of cancer in whales, as well as in most groups of animals that develop cancer, including most mammals, is roughly similar to that in mice [18, 19, 89, 90]. Actually, the incidence of cancer in the blue whale as well as in other large cetaceous seems to be even lower than that observed in most common mammals [91, 92]. Similar considerations could be made concerning benign tumors. Therefore, *the incidence of neoplasms, either malignant or benign, is not a simple function of protoplasm cell mass at risk per unit time.*

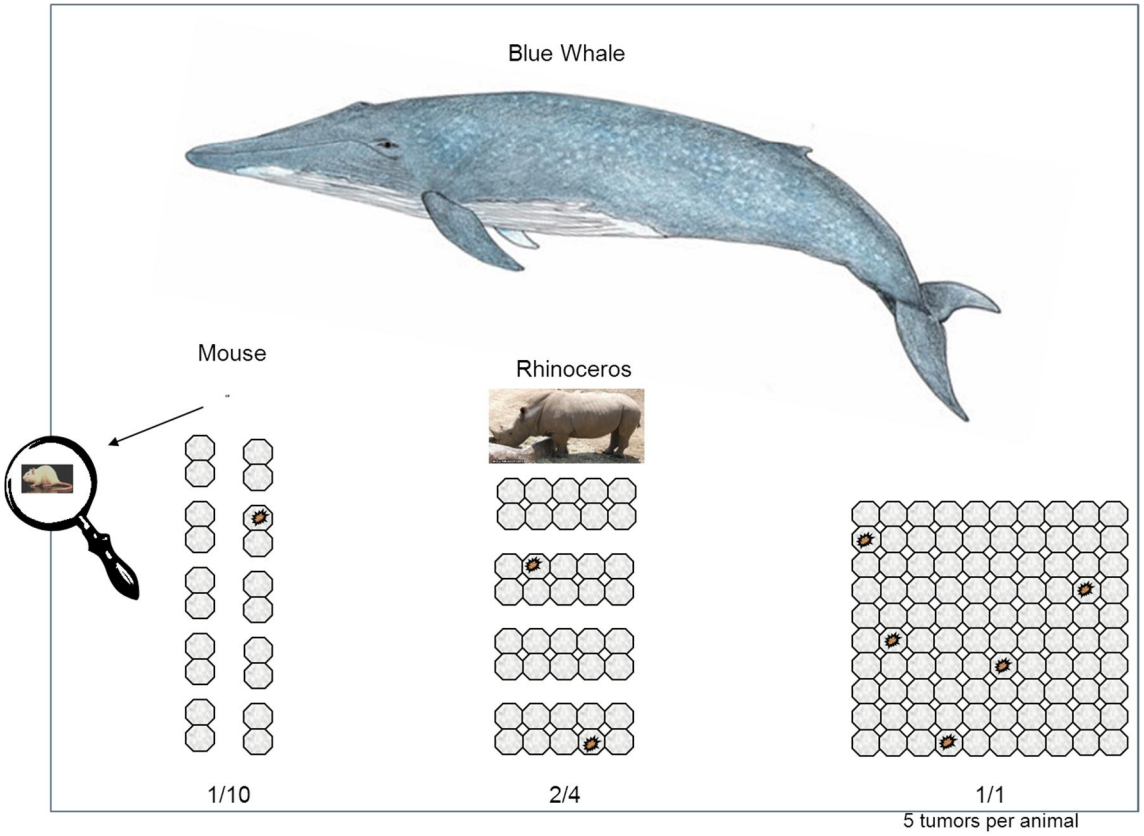

FIGURE 2: Relative size of mouse (about 30 g), rhinoceros (about 2 tons) and blue whale (about 100 tons) and theoretical influence that size of whole body, organ or tissue would have on tumor incidence per unit time on the assumption that the individual cell in an organ or tissue is the unit at risk of carcinogenesis. We have arbitrarily assumed that a carcinogenic mutation occurs at a rate of 1 per 20 cells units per unit time (tumor cells are identified with a mark inside the cell) and in consequence, animals with 2, 10 and 100 cells should develop, respectively, 1 neoplasm in every 10 animals, 2 neoplasms in every 4 animals and 5 neoplasms per animal, per unit time. The correspondence between animals (mouse, rhinoceros and blue whale) and number of cells (2, 10 and 100, respectively) is only illustrative. The figure was inspired in Dawe (quotation 31).

Some ad hoc hypotheses have been invoked to account for this fact on the assumption that *the individual cell in an organ or tissue is the unit at risk of carcinogenesis*. For example, the animal fat depots might sequester fat-soluble carcinogens with efficiency proportional to animal's size and thereby proportionately diminish the exposure of other tissues. Other putative explanations hold that the evolution has equipped larger animals with extra tumor suppressor genes or with efficient defenses against cancer that could be proportional to animal size, such as mechanisms of DNA repair, cellular resistance to mutagenic activation of putative carcinogens, immunological surveillance, etc. [93-97]. However, these invoked mechanisms remain largely undemonstrated as general rules and in fact there is evidence that argues against some of these possibilities: for example, numerous studies on DNA repair allele polymorphisms have failed to provide any evidence of association with cancer risk [93].

Is cancer a disorder of the individual cell?

On the contrary, the hypothesis of cancer that we present in this essay could offer, at least in principle, a relatively easy solution of the riddle by assuming that *the true basic unit at risk of carcinogenesis is the tissue or organ as a whole rather than the individual cell*. In effect, according to this hypothesis, cancer originates in organs or tissues that display a significant decline of their regenerative capacities, and this would occur when a critical proportion of their cells have partially or wholly lost that capacity. In such a case, if an organ were x times larger than another one, the probability that its regenerative capacity is critically diminished would be x times lower, because an x times greater number of cells would have to be affected to depress that capacity. This lower probability would balance the proportionally higher number of their cells that could be transformed. As a result, if the unit at risk is, for example, one liver rather than 10^9 (mouse) as opposed to 3×10^{15} (blue whale) liver cells, then the whale will be at no greater risk of developing liver cancer than the mouse or any other animal with an equally efficient defense mechanism against cancer. A similar conclusion can be attained if the true basic unit at risk of carcinogenesis is a part of a tissue or organ rather than the tissue or organ as a whole.

However, this interpretation may be not the whole story. In effect, it can explain the fact that animals with extremely different body sizes exhibit similar rates of tumor incidence by unit of time but the whole story also demands to explain a similar tumor incidence by unit of lifespan. In effect, in the case of the blue whale and the mouse our hypothesis may account for the fact that the blue whale has not a higher tumor incidence than that of the mouse by unit time, for example during the mouse's lifespan, that is, 2 years. However, the blue whale lives 40 times more than the mouse (ratio lifespan of blue whale/ lifespan of mouse = 80/2 years = 40) and in consequence, the blue whale should, even accepting our hypothesis, develop 40 times more cancers during its life than the mouse.

Metabolism and cellular activity

The concept of basal metabolic rate (BMR) can be a useful tool to account for this problem. BMR is the rate of energy expenditure per unit time by endothermic animals at rest and accounts for about 60-70% of the daily caloric expenditure by individuals. Large animals have higher total BMR than smaller ones but the BMR at the cellular level (mass-specific BMR or msBMR) is much lower. In effect, according to the Max Kleiber's law [98, 99], msBMR diminishes with body weight according to a mathematical principle called quarter-power scaling. For example, a cat that is 100 times more massive than the mouse, displays a msBMR about $100^{1/4}$ (= 3.2) times lower than that of mouse. In the same way, the blue whale, that is about 3×10^6 times more massive than the mouse, displays a msBMR that is approximately equal to $(3 \times 10^6)^{1/4}$ (about 40) times lower than that exhibited by the mouse. The reduction of msBMR with increased body size has been demonstrated in vivo. Some years ago, Wheatley and Clegg [100] suggested that this reduction is associated with the rate of delivery of both essential nutrients to cells and substrates to enzymes at the intracellular level, in the space of the organism, and that this effect should be absent under culture conditions, when the cells are removed from the influence of the body. This prediction was confirmed some years later by Brown et al. [101] who

demonstrated that neither metabolic rate nor the maximal activities of key enzymes of oxidative or anaerobic metabolism scaled significantly with donor body mass in cultured cells, indicating the absence of intrinsic, species-specific, cellular metabolic rate set points.

Metabolism generates oxygen radicals that are considered to contribute to cellular aging as well as to potential oncogenic mutations [102, 103]. In consequence, the blue whale that exhibits a msBMR about 40 times lower than that of mouse should age about 40 times slower than the mouse and in consequence the time for individual cells to get the natural decline in regenerative ability observed with aging and the time to get potential neoplastic mutations should be, in the blue whale, 40 times slower than in the mouse. Taking into account that the ratio between lifespan of blue whale and mouse is really 40, then, we could explain why the tumor incidence in the blue whales along their long lifespan (80 years) may be not higher to that observed in mice along their short life (2 years).

In summary, considering the hypothesis that cancer originates only in organs or tissues (or parts of them) that display a significant decline of their regenerative capacities together with the notion that the msBMR diminishes according to the quarter-power scaling, we can understand why the blue whale may not display a higher tumor incidence than that of the mouse, by unit of lifespan, that was what we wanted to demonstrate.

This reasoning may be extended to most mammals exhibiting widely differences in body size and lifespan that range over nine orders of magnitude and 80 times, respectively [20, 89, 91, 104-116]. In effect, as shown in **TABLE 1,** the real incidence of cancer observed in more than forty different mammal species is, in all cases, strikingly lower than that predicted *by assuming the individual cell as the unit of carcinogenesis*, either considering cells of all species displaying similar or different msBMR. This difference between theory and reality tends to become astronomical as larger animals are considered.

Towards a synthesis of these ideas

In contrast, the real cancer incidence is, in most cases, very similar to that predicted *by assuming the organ (or part of it) as the unit of carcinogenesis* especially if we include into the hypothesis, the concept that msBMR decreases progressively as body mass increases, according to Kleiber's law.

Exceptional cases that do not fit completely to the general scheme described above, such as the elephant, the bowhead whale or the naked mole rat that display a significantly lower tumor incidence than that observed in most mammals, might also be understood by incorporating to the general scheme, the existence of particular mechanisms aimed to allow these animals to preserve the organ integrity and/or their regenerative ability quite efficiently throughout their lives. In fact, powerful mechanisms that protect from DNA damage, as invoked to be acting in elephants and bowhead whales, have been associated with protection against tissue damage [20, 117, 118]. Similarly, different studies have suggested that the high-molecular-mass

Hyaluron secreted by naked mole rat's cells, as well as other mechanisms, would protect these animals against stressors and prevent oxidative damage accrual and the translation of these potentially high levels of damage into a decline in normal function [110, 119,120]. Another two exceptions could be the blue whale, whose cancer incidence seems to be modestly lower than that of the mouse, and the human being. Actually, the human does not display a lower tumor incidence than most mammals but the predicted value - even considering the organ as unit of carcinogenesis and the real msBMR of our species - is significantly higher than the observed tumor incidence. This difference can be attributed to the fact that the predicted value is dependent to the lifespan of each species and the human displays a lifespan that is many times longer than that expected according to its mass-specific BMR.

Cancer as a disorder of cellular society

The idea that cancer is an organ or tissue disease rather than a cellular one has been advocated by Waddington, Smithers and others many years ago [2, 121] and, more recently, by the group of Sonnenschein and Soto with their tissue organization field theory (TOFT) of cancer [84, 122]. In agreement with this interpretation, Sigston and Williams [123] have recently proposed the idea that cancer may be the emergence of a new 'system' arising from the tissue components of a functional tissue unit or part that has experienced an alteration of its normal self-organization arrangement and function.

The notion that other diseases – beyond cancer – may also be organ or tissue-based pathologies rather than cellular ones, is supported, for example, by the interpretation of rheumatoid arthritis advocated by Reines [124] in which this syndrome is considered the clinical manifestation of an underlying attempt to regenerate damaged or aged cartilage and sub-chrondal bone in an adult organism.

Competing interests

The authors declare no competing interests.

Authors' contributions

The two authors contributed equally to this work and they read and approved the final manuscript.

Acknowledgements

We are grateful to Dr Richmond T. Prehn, Dr Miguel A. Basombrío and Dr Carlos M. Galmarini for their helpful and critical discussion of the manuscript. This work was supported by CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas,Argentina). Both authors are members of the Research Career, CONICET.

This article is dedicated to the memory of an intelligent, honest and extraordinarily generous man, Dr. Richmond T. Prehn, Father of Modern Tumor Immunology, who passed away peacefully at his house in Seattle last November close to turning 94 years old.

References

1. Boveri T (1929). *The origin of malignant tumors*. Williams and Williams, Baltimore MD.

2. Waddington CH (1935). Cancer and the theory of organisers. *Nature***135**: 606-608.

3. Warburg O (1956). On the origin of cancer cells. *Science***123**: 309-314.

4. Bishop JM (1980). The molecular biology of RNA tumor viruses: a physician's guide. Basic science for clinicians. *N Engl J Med* **303:**675-682.

5. Hanahan D, Weinberg RA (2000). The hallmarks of cancer. *Cell* **100:**57-70.

6. Bignold LP (2002): The mutator phenotype theory can explain the complex morphology and behavior of cancer**.** *Cell Mol Life Sci* **59:** 950-958.

7. Frank SA (2005): Age-specific incidence of inherited versus sporadic cancers: a test for the multistage theory of carcinogenesis. *Proc Natl Acad Sci USA* **102:**1071-1075.

8. Zhu K, Liu Q, Zhou Y, Tao C, Zhao Z, Sun J, Xu H (2015). Oncogenes and suppressor genes: comparative genomics and network perspectives. *BMC Genomics* **16** *(*Suppl 7): S8.

9. Tomasetti C, Marchionni L, Nowak MA, Parmigiani G, Vogelstein B (2015). Only three driver gene mutations are required for the development of lung and colorectal cancers. *Proc Natl Acad Sci USA* **112**: 118-123.

10. Duesberg P, Rasnick D (2000). Aneuplody, the somatic mutation that makes cancer a species of its own**.** *Cell Motil Cytoskel* **47:**81-107.

11. Sonnenschein C, Soto AM (2000): Somatic mutation theory of carcinogenesis: why it should be dropped and replaced**.** *Mol Carcinogenesis* **29:**205-211.

12. Prehn RT(2005).The role of mutation in the new cancer paradigm. *Cancer Cell Int* **5:** 9-14.

13. Sonnenschein C, Soto AM (2015). Cancer metastases: So close and so far. *J Natl Cancer Inst* **107:** djv 236.

14. Danthala M, Gundeti S, Kuruva SP, Puligundla KC, Adusumilli P, Karnam AP, Bala S, Konatam ML, Maddali LS, Digumarti RR (2017). Generic Imatinib in chronic myeloid leukemia: survival of the cheapest. *Clin Lymphoma Myeloma Leuk* **17**: 457-462.

15. Bailar JC III, Gornik HL (1997). Cancer undefeated**.** *N Engl J Med* **336:**1569-1574.

16. Talmadge JE, Singh RK, Fidler IJ, Raz A (2007). Murine models to evaluate novel and conventional therapeutic strategies for cancer. *Am J Pathology* **170**: 793-804.

17. Siegel RL, Miller KD, Jemal A (2017). Cancer Statistics, 2017. *CA Cancer J Clin* **67**: 7-30.

18. Caulin AF, Maley CC. Peto's paradox (2011): evolution's prescription for cancer prevention. *Trends Ecol Evol* **26**: 175-182.

19. Bredberg A (2011). Cancer: more of polygenic disease and less of multiple mutations? A quantitative viewpoint. *Cancer* **117**: 440-445.

20. Abegglen LM, Caulin AF, Chan A, Lee K, Robinson R, Campbell MS et al. (2015). Potential mechanisms for cancer resistance in elephants and comparative response to DNA damage in humans. *JAMA* **314**: 1850-1860.

21. Peto R (1977). Epidemiology, multistage models, and short-term mutagenicity tests. In: *The Origins of Human Cancer*. Cold Spring Harbor Conferences on Cell Proliferation. **4**. Cold Spring Harbor Laboratory. pp. 1403–1428.

22. Ruggiero, R.A. and Bustuoabad, O.D. (2006). The biological sense of cancer: a hypothesis. *Theor Biol Med Mod* **3**: 43.

23. Ruggiero, R.A., Bustuoabad, O.D., Chiarella, P., Bruzzo, J. and Meiss, R.P. (2008). On the Biological Significance of Tumor Growth. In: *Cell Growth Processes: New Research* (ed. D. Kimura). Nova Science Publishers, NY, pp. 89-121.

24. Prehn RT (1997). Regeneration versus neoplastic growth. *Carcinogenesis* **18:**1439-1444.

25. Zajicek G (1996). A new cancer hypothesis. *Med Hypoth* **47:**111-115.

26. Kenny PA, Bissell MJ (2003).Tumor reversion: correction of malignant behavior by microenvironmental cues. *Int J Cancer* **107:**688-695.

27. Maffini MV, Soto AM, Calabro JM, Ucci AA, Sonnenschein C (2004).The stroma as a crucial target in rat mammary gland carcinogenesis. *J Cell Sci* **117:**1495-1502.

28. Bizzarri M, Cucuna A (2016). SMT and TOFT: Why and how they are opposite and incompatible paradigms. *Acta Biotheor* **64**: 221-239.

29. Wellings SR (1969). Neoplasia and primitive vertebrate phylogeny: echinoderms, prevertebrates and fishes. A review. *Natl Cancer Inst Monograph* **31:**59-128.

30. Sparks AK (1969). Review of tumors and tumor-like conditions in Protozoa, Coelenterata, Platyhelminthes, Annelida, Sipunculida and Arthropoda excluding Insects. *Natl Cancer Inst Monograph* **31:**671-682.

31. Dawe CJ (1969). Phylogeny and oncogeny. *Natl Cancer Inst Monograph* **31:**1-40.

32. Walker CW, Boom JDG, Marsh AG (1992). First non-vertebrate member of the *myc* gene family is seasonally expressed in an invertebrate testis. *Oncogene* **7:**2007-2012.

33. Robert J (2010). Comparative study of tumorigenesis and tumor immunity in invertebrates and nonmammalian vertebrates. *Dev Comp Immunol* **34**: 915-925.

34. Tascedda F, Ottaviani E (2014). Tumors in invertebrates. *ISJ* **11**: 197-203.

35. Martinez-Acosta VG, Zoran MJ (2015). Evolutionary Aspects of Annelid Regeneration. eLS; doi:10.1002.

36. Hall F, Morita M, Best JB (1986). Neoplastic transformation in the planarian: Cocarcinogenesis and histopathology. *J Exp Zool* **240:**211-227.

37. Saló E (2006). The paper of regeneration and the stem cell kingdom: freshwater planarias (Platyhelmintes). *Bioessay* **28**: 546-559.

38. Del Rio-Tsonis K, Tsonis PA (1992). Amphibian tissue regeneration: a model for cancer regulation (review). *Int J Oncol* **1:**161-164.

39. Oviedo NJ, Beane WS (2009). Regeneration: the origin of cancer or a possible cure. *Semin Cell Dev Biol* **20**: 557-564.

40. Zamaraev VN (1974). Does regenerative capacity decrease with age? *Sov J Dev Biol* **4:** 495-503.

41. Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008). Wound repair and regeneration. *Nature* **453**: 314-321.

42. Taylor RL (1969). Formation of tumor-like lesions in the cockroach *Leucophaea maderae* after decapitation. *Natl Cancer Inst Monograph* **31:**419-432.

43. Cooper EL(1976). Immunity and neoplasia in Mollusks. *Isr J Med Sci* **12**: 479-494.

44. Lopez A (1979). Tumoral pathology in spiders. *J Invertebr Pathol* **34:**224-230.

45. Mechler BM, Strand D, Kalmes A, Merz R, Schmidt M, Torok I (1991). Drosophila as a model system for molecular analysis of tumorigenesis. *Environ Health Perspect* **93:** 63-71.

46. Zilakos NP, Tsonis PA, Del Rio-Tsonis K, Parchment RE (1992). Newt squamous carcinoma proves phylogenetic conservation of tumors as caricatures of tissue renewal. *Cancer Res* **52:**4858-4865.

47. Poinar GO(1992). Immune responses and wound repair. In *Diseases of Nematodes. vol 1*, p.133-40, CRC Press, Boca Raton, Florida.

48. Berry LW, Wertlund B, Schedl T (1997). Germ-line tumor formation caused by activation of glp-1, a Caenorhabditis elegans member of the Notch family of receptors. *Development* **124**: 925-936.

49. Sánchez J, Kuba L, Berón-vera B, Dans SL, Crespo EA, Van Bressem MF, Coscarella MA, García NA, Koen Alonso M, Pedraza SN, Mariotti PA (2002). Uterine adenocarcinoma with metastasia in a bottlenose Tursiops truncatus from northern Patagonia, Argentina. *Dis Aquat Org* **48**: 155-159.

50. Ostrander GK, Cheng KC, Wolff JC, Wolfe MJ (2004). Sharks, cartilage, cancer and the growing threads of pseudoscience. *Cancer Res* **64**: 8485-8491.

51. Caussinus E, Gonzalez C (2005). Induction of tumor growth by altered stem-cell asymmetric división in Drosophila melanogaster. *Nature Genet* **37:**1027-1028.

52. Smolarz K, Renault T, Wolowicz M (2006). Ultrastructural study of neoplastic cells in Macomabalthica (Bivalvia) from the Gulf of Gdansk (Polland). *J Invertebr Pathol* **92**: 79-84.

53.Kiriakakis E, Markaki M, Tavemarakis N (2015). Caenorhabditis elegans as a model of cancer research. *Mol Cell Oncol* **2** (2): e975027.

54. Kitagawa M, Utsuyama M, Kurata M, Yamamoto K, Yuasa Y, IshikawaY, Arai T, Hirokawa K (2005): Cancer and aging: symposium of the 27th annual meeting of the Japanese society for biomedical gerontology. *Tokyo Cancer Immunol Immunother* **54:** 623-634.

55**.** Falandry C, Bonnefoy M, Freyer G, Gilson E (2014). Biology of cancer and aging: a complex association with cellular senescence. *J Clin Oncol* **32**: 2604-2610.

56. Braun H, Schmidt BMW, Raiss M, Baisantry A, Mircea-Constantin D, Wang S, Gross ML, Serrano M, Schmitt R, Melk A (2012). Cellular senescencelimits regenerative capacity and allograft survival. *J Am Soc Nephrol* **23**: 1467-1473.

57. Campisi J (2013). Aging, cellular senescence and cancer. *Annu Rev Physiol* **75**: 685-705.

58. Bathia-Dey N, Kanherkar RR, Stair SE, Makarev EO, Csoka AB (2016). Cellular senescence as the causal nexus of aging. *Frontiers Genet* **7**: 13.

59. Karin M, Lawrence T, Nizet V (2006). Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* **124:** 823-836.

60. Harrison SA, Bacon BR (2005). Relation of hemochromatosis with hepatocellular carcinoma: epidemiology, natural history,
pathophysiology, screening, treatment and prevention. *Med*

Clin North Am **89:** 391-409.

61. Raman JD, Nobert CF, Goldstein M (2006). Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. *J Urol* **174**: 1819-1822.

62. Sharpless NE, DePinho RA (2004). Telomeres, stem cells, senescence and cancer. *J Clin Invest* **113:**160-168.

63. Haddow A (1938). Cellular inhibition and the origin of cancer. *Acta Unio Int Contra Cancrum* **3:** 342-352.

64. Farber E, Rubin H (1991). Cellular adaptation in the origin and development of cancer. *Cancer Res* **51:**2751-2761.

65. Farber E (1995): Cell proliferation as a major risk factor for cancer: a concept of doubtful validity. *Cancer Res* **55:**3759-3762.

66. Simpson CJ, Bissell MJ, Werb Z (1995). Mammary gland tumor formation in transgenic mice overexpressing stromelysin-1. *Semin Cancer Biol* **6:**159-163.

67. Kuraisky A, Karin M, Grivennikov SI (2011). Tumor promotion via injury-and death-induced inflammation. *Immunity* **35**: 467-477.

68. Duke JM, Bauer J, Fear MW, rea S, Wood FM, Boyd J (2014). Burn injury, gender and cancer risk: population-based cohort study using data from Scotland and Western Australia. *BMJ* **4** (1): e 003845.

69. Goldkorn T, Filosto S, Chung S (2014). Lung injury and lung cancer caused by cigarette smoke-induced oxidative stress: Molecular mechanisms and therapeutic opportunities involving the ceramide-generating machinery and epidermal growth factor receptor. *Antioxid Redox Signal* **21**: 2149- 2174.

70. Tyagi V, Theobald J, Barger J, Bustoros M, Bayin NS, Modrek AS, Kader M, Anderer EG, Donahue B, Fatterpekar G, Placantonakis DG (2016).Traumatic brain injury and subsequent glioblastoma development: Review of the literature and case reports. *Surg Neurol Int* **7**: 78.

71. Meiss RP, Novelli JE, Abalo E, Larusso A, Gualtieri A. Bianco M et al (2017). Breast cancer thirty years later: a comparative study between a 1983-1984 and a 2012-2013 cohorts of argentine women. *J Can Epi Treat* **1**: 1-10.

72. Dvorak HF (1986).Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* **315:**1650-1691.

73. Schafer M, Werner S (2008). Cancer as an overhealing wound: an old hypothesis revisited. *Nat Rev Mol Cell Biol* **9**: 628-638.

74. Dvorak HF (2015). Tumors: wounds that do not heal-Redux. *Cancer Immunol Res* **3**: 1-11.

75. Nery R (1976). Carcinogenic mechanisms: a critical review and a suggestion that oncogenesis may be adaptive ontogenesis**.** *Chem Biol Interact* **12:**145-169.

76. Chene G, Tchirkov A, Pierre-Eymard E, Dauplat J, Raoelfils I, Cayre A, Watkin E, Vago P, Penault-LClorca F (2013). Early telomere shortening and genomic instability in tubo-ovarian preneoplastic lesions. *Clin Cancer Res* **19**: 2873-2782.

77. Shaw JA, Graham TA, Stebbing J (2013). Genomic instability in pre-neoplastic colonic lesions. *Oncogene* **32**: 5331-5332.

78. Schindel DT, Grosfeld JL (1997). Hepatic resection enhances growth of residual intrahepatic and subcutaneous hepatoma, which is inhibited by octreotide. *J Pediatr Surg* **32:** 995-998.

79. Alspach E, Fu Y, Stewart SA (2013). Senescence and the pro-tumorigenic stroma. *Crit Rev Oncog* **18**: 549-558.

80. Ohtani N, Hara E (2013). Roles and mechanisms of cellular senescence in regulation of tissue homeostasis. *Cancer Science* **104**: 525-530.

81. Martínez-Jiménez CP, Eling N, Chen HC, Vallejos CA, Kolodziejczyk AA, Connor F et al. (2017). Aging increases cell-to-cell transcriptional variability upon immune stimulation. *Science* **355**: 1433-1436.

82. Ban N, Kai M (2009). Implications of replicative stress-related stem cell aging in radiation-induced murine leukemia. *Br J Cancer* **101**: 363-371.

83. Ewing J (1940). *Neoplastic Disease: a Treatise on Tumors* Philadelphia: Saunders.

84. Sonnenschein C, Soto AM (1999): *The Society of Cells.* New York: Springer-Verlag.

85. Furth J (1953). Conditioned and autonomous neoplasms: a review. *Cancer Res* **13:** 477-492.

86. Peto R, Roe FJC, Lee PN, Levy L, Clack J. (1975). Cancer and ageing in mice and men. Br J *Cancer* **32**: 411–426.

87. Andervont HB, Dunn TB (1962). Occurrence of tumors in wild house mice. *J Natl Cancer Inst* **28:**1153-1163.

88. Gardner MB, Henderson BE, Rongey RW, Estes JD, Huebner RJ (1973). Spontaneous tumors of aging wild house mice, incidence, pathology and C-type virus expression. *J Natl Cancer Inst* **50**: 719-734.

89. Madsen T, Arnal A, Vittecoq M, Bernex F, Abadie J, Labrut S et al. (2017). Cancer prevalence and etiology in wild and captive animals. In: *Ecology and Evolution of Cancer*, (Ed. B Ujvari, B Roche and F Thomas), Chapter 2, pp. 11-46, Academic Press.

90. Sneed A (2014). How big animals deter cancer. *Sci Am* **311**: 28.

91. Newman SJ, Smith SA (2006). Marine mammal neoplasia: a review. *Vet Pathol* **43**: 865-880.

92. Speight M (2015). An investigation into cancer resistance in cetaceous. A thesis submitted in partial-fulfilment of the requirements for the degree of Master of Research at Imperial College London.

93. Vineis P, Manuguerra M, Kavvoura FK, Guarrera S, Allione A, Rosa F et al. (2009). A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. *J Natl Cancer Inst* **101**: 24-36.

94. Rudo K, Meyers WC, Dauterman W, Langenbach R (1987): Comparison of human and rat hepatocyte metabolism and mutagenic activation of 2-acetylaminofluorene. *Cancer Res* **47:** 5861-5867.

95. Hsu IC, Harris CC, Lipsky MM, Snyder S, Trump BF (1987). Cell and species differences in metabolic activation of chemical carcinogens. *Mutat Res* **177:**1-7.

96. Hahn WC, Weinberg RA (2002). Rules for making human tumor cells. *N Engl J Med* **347:**1593-1603.

97. Holliday R (2006). Aging is no longer an unsolved problem in biology. *Ann N Y Acad Sci* **1067:**1-9.

98. Kleiber M (1947). Body size and metabolic rate. *Physiol Rev* **27**: 511-541.

99. Takemoto K, Li M, Nishizuka SS (2016). Importance of metabolic rate to the relationship between the number of genes in a functional category and body size in Peto's paradox for cancer. *R Soc Open Sci* **3** (9): 160267.

100. Wheatley DN, Clegg JS (1994). What determines the basal metabolic rates of vertebrates in vivo? *Biosystems* **32**: 83-92.

101. Brown MF, Gratton TP, Stuart JA (2007). Metabolic rate does not scale with body mass in cultured mammalian cells. *Am J Physiol* **292**: R2115-R2121.

102. Dang CV (2012). Link between metabolism and cáncer. *Genes Dev* **26**: 877-890.

103. Liochev SI (2013). Reactive oxygen species and the free radical theory of aging. *Free Radic Biol Med* **60**: 1-4.

104. Uno H (1997). Age-related pathology and biosenescent markers in captive Rhesus Macaques. *Age* **20**: 1-13.

105. Follmi J (2005). Symptoms, radiographic examinations and pathologies: development of a scoring system to evaluate physical condition and quality of life in geriatric zoo mammals. Doctoral thesis, University of Bern.

106. Munson L, Moresco A (2007). Comparative pathology of mammary gland cancers in domestic and wild animals. In: *Comparative Pathobiology of breast cancer*. (Ed: RD Cardiff), pp.7-22, IOS Poress, Amsterdam.

107. Owston MA, Ramsay EC, Rotstein DS (2008). Neoplasia in felids at the Knoxville Zoological Gardens *J Zoo Wildlife Med* **39**: 608-613.

108. De Magalhaes JP, Costa J (2009). A database of vertebrate longevity records and their relation to other life-history traits. *J Evol Biology* **22**: 1770-1770.

109. Sasieni PD, Shelton J, Ormiston-Smith N, Thomson CS, Silcocks PB (2011). What is the lifetime risk of developing cancer? The effect of adjusting for multiple primaries. *Br J Cancer* **105**: 460-465.

110. Tian X, Azpura J, Hine C, Vaidya A, Myakishev-Rempel M, Ablaeva J et al (2013). High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. *Nature* **499**: 346-349.

111. Hermes R, Goritz F, Saragusty J, Stoops MA, Hildebrandt TB (2014). Reproductive tract tumors: the scourge of woman reproduction ails indian rhinoceroses. *PLoS One* **9** (3): e92595.

112. Hamano T, Terasawa F, Tachikawa Y, Murai A, Mori T, El-Dakhly K et al. (2014). Squamous cell carcinoma in a Capybara (Hydrochoerus hydrochaeris). *J Vet Med Sci* **76**: 1301-1304.

113. Junginger J, Hansmann F, Herder V, Lehmbecker A, Peters M, Beyerback M et al. (2015). Pathology in captive felids at German Zoological Gardens. *PLoS One* **10** (6): e0130573.

114. Lair S, Measures LN, Martineau D (2016). Pathologic findings and trends in mortality in the beluga (Delphinapterus leucas) population of the St Lawrence estuary, Quebec, Canada, from 1983 to 2012. *Vet Pathol* **53**: 22-36.

115. Abeer AM, Zakia AM, Muna EA, Afat EA (2016). Incidence of multiple mammary tumors and fibro-adenoma in pathological studies of udder affections in camel (Camelus dromedarius). *J Cancer and Tumor International* **4**: 1-7.

116. Taylor KR, Milone NA, Rodríguez CE (2016). Four cases of spontaneous neoplasia in the naked mole-rat (Heterocephalus glaber), a putative cancer-resistant species. *J Gerontol A Biol Sci Med Sci* **72**: 38-43.

117. Jackson SP, Bartek J (2009). The DNA-damage response in human biology and disease. *Nature* **461**: 1071-1078.

118. Keane M, Semeiks J, Webb AE, Li Y, Quesada V, Craig T et al. (2015). Insights into the evolution of longevity from the Bowhead Whale genome. *Cell Rep* **10**: 112-122.

119. Lewis KN, Mele J, Hornsby PJ, Buffenstein R (2012). Stress resistance in the naked mole-rat: the bare essentials – a mini-review. *Gerontology* **58**: 453-462.

120. Skulachev VP, Holtze S, Vyssokik H, Bakeeva LE, Skulachev MV, Markov AV et al (2017). Neoteny, prolongation of youth: from naked mole rats to “naked apes” (humans). *Phisiol Rev* **97**: 699-720.

121. Smithers DW (1962). An attack to cytologism. *Lancet* **1**: 493-499

122. Sonnenschein C, Soto AM (2016). Carcinogenesis explained within the context of a theory of organisms. *Prog Biophys Mol Biol* **122**: 70-76.

123. Sigston EAW, Williams BRG (2017). An emergence framework of carcinogenesis. *Front Oncol* **7**: 198.

124. Reines B (2004). Is rheumatoid arthritis premature osteoarthritis with fetal-like healing? *Autoimmun Rev* **3**: 305-311.