Editorial

# Ecology and games in cancer: new insights into the disease

Claudia Manini[1,2], José I. López[3]

[1] Department of Pathology, San Giovanni Bosco Hospital, Turin, Italy; [2] Department of Sciences of Public Health and Pediatrics, University of Turin, Turin, Italy; [3] Biomarkers in Cancer Unit, Biocruces-Bizkaia Health Research Institute, Barakaldo, Spain

## Introduction

Cancer is a complex, dynamic disease that is under permanent study by basic scientists, oncologists, pathologists, and other specialists. The different ways by which cancers evolve need to be understood if we are to improve the implementation of successful therapeutic responses based on precision medicine. There has been huge investments in massive genomic analyses in recent years, seeking to decipher the intricacies of this disease. However, current evidence shows a need for wider scientific assessment extending beyond knowledge of cancer itself. Here, we introduce medical specialists working on cancer to some new insights into the disease which may eventually improve treatments in the near future.

## Ecology

Ecology, for example, has improved our understanding of how intratumor heterogeneity develops. Indeed, the term eco-oncology has been coined as a result of this new integration of science from different areas [1]. Considering tumors as communities of individuals (cells) which are able to cooperate or not depending on specific contexts or interests is a significant step forward in this process [2]. This has led some authors to suggest that deciphering cancer's secrets is more than a pure technological problem and that cancer should be also thought of as a sort of social dysfunction[3]. This approach opens up promising new prospects for envisaging the evolutionary dynamics of tumors under ecological principles [4,5].

Pathologists analyze and diagnose tumors exactly when they are sampled or removed from patients. Knowing where a tumor comes from, where it is going in terms of evolution and how is not part of a pathologist's remit. Evolutionary studies have shown that two different tumors may be identical at a precise time of their respective evolutions [6], so the histological images observed by a pathologist and the molecular landscape detected by next-generation sequencing, for example, should be considered as mere static snapshots of a unique moment in evolution. The design of mathematical algorithms for inferring phylogenetic events in the past seeks to overcome this limitation [7]. The application of such tools to a whole genome sequencing of 95 biopsies of 33 clear cell renal cell carcinomas has demonstrated the timing of events in the devel-

**How to cite this article:** Manini C, López JI. Ecology and games in cancer: new insights into the disease. Pathologica 2022;114:347-351. https://doi.org/10.32074/1591-951X-798

opment of such tumors [8]. More specifically, this work shows that the oncogenesis of this neoplasm begins with a simultaneous 3p loss and 5q gain in one allele as early as childhood and adolescence. Dormant cells affected by this initial chromothripsis alteration, usually no more than a few hundred in number, develop the neoplasm 50 or 60 years later when the *VHL* gene in the other allele mutates[8].

From an eco-evolutionary viewpoint, three tumor models following Darwinian-type patterns have been described: Linear, branching, and punctuated [9]. Linear evolution is a step-wise process in which new driver mutations confer stronger selective advantages to the tumor at every successive step. Branching evolution refers to the different clones generated from a common ancestor evolving in parallel. In punctuated evolution, however, a clone with high fitness fixes early in the tumor evolution, dominating future tumor expansion. We know that Darwinian forces impact the phenotypic diversity of tumors through microenvironmental pressures, for example via hypoxia. However, such forces do not act directly on tumor genotypes, and in this there is a fundamental difference that may explain the divergences observed between phenotypic and genotypic intratumor heterogeneities. A paradigmatic example of this phenotypic/genotypic divergence is neutral tumor evolution, the fourth, non-Darwinian model of tumor evolution [9], where a huge number of passenger mutations occur with no apparent phenotypic variations. For example, an exhaustive genomic study of 286 regions in a single hepatocellular carcinoma has found more than 100 million mutations in codifying regions [10].

Interestingly, the same tumor type may evolve differently in different patients. Clear cell renal cell carcinomas, for example, may follow either punctuated, branching, or even neutral evolutionary patterns [11]. As recently proved, this issue matters in terms of prognosis because punctuated tumors have been shown to behave aggressively with early multiple metastases, whereas tumors displaying a branching-type evolution follow an attenuated clinical course with late solitary metastases, and neutral-type tumors behave indolently, without metastasis [11].

Fitness is an ecological concept that defines the capacity of an individual to transmit their genes to their progeny. In cancer, fitness describes the capacity of a malignant cell to grow, invade, and metastasize. These are all mechanisms that ensure cancer cell survival, so in clinical practical terms, the greater the fitness, the greater the tumor malignancy. Increasing aggressiveness, however, increases the metabolic cost, i.e. energy expenditure. Energy is a finite resource in nature which can be quantified in biological systems by calculating the Atkinson level [12]. In normal conditions, malignant cells spend all their energy on increasing their fitness, i.e. on fueling cellular growth, mitotic division, and motility abilities to carry out programmed processes such as tumor invasion and metastasis.

At this point, ecological principles provide new insights into cancer treatment [13]. Under conventional treatment conditions, drugs are administered following the maximum tolerable dose strategy. As a result, malignant cells are forced to deviate all their energy from increasing their fitness to developing drug resistance. The practical conclusion using the maximum tolerable dose strategy is that resistance will soon be reached and the tumor will transform inevitably into a resistant-to-therapy neoplasm with dire consequences for the patient. However, a theoretical approach to the problem indicates that a dose below the maximum tolerable will push cells to choose between the two decisive, mutually exclusive tasks of developing the malignant phenotype (invasion, metastases) and generating resistance to therapy. If this is so, cells exposed to doses below the maximum tolerable will slow down in both tasks due to the finite amount of energy available in the cell. The conclusion is that dividing energy expenditure into two different tasks delays both of them, so aggressiveness and tumor resistance are both expected to appear later.

Parrondo's paradox [14] is an anti-intuitive algorithm initially developed in physics and engineering which states that two losing strategies may win when combined. This paradox, it has been applied to evolutionary biology [15] and cancer [16] with interesting results. Applied to cancer therapy, for example, the strategy consists of two games played by a tumor cell after successively tossing a coin (head/tail) to make decisions. Strategy A (head) means the administration of a fake drug while strategy B (tail) indicates the administration of the correct drug. The use of a fake drug in strategy A introduces the concept of an ersatzdroge (from the late 19th-century German *ersatz*, meaning replacement) proposed by Kim et al. [17] in 2015. This term refers to the use of a non-toxic drug that competes with the cytotoxic agent in the ATP-binding cassette transportation system which in physiological conditions externalizes the cytotoxic agent present in the cell, thus reducing its intracellular concentration. The result of such competition between fake and real drugs to secure the transporter for themselves generates a higher intracellular concentration of the real drug. The stochastic chaos underlying the application of Parrondo's paradox to cancer therapy suggests that tossing a coin repeatedly to decide whether to apply strategy A or B will lead to a successful result. In the context of cancer, success is measured as longer survival.

In the end, Parrondo's paradox proposes a sort of tumor containment through the administration of doses below the maximum tolerable via the alternating of fake and real drugs. In the same sense, a tumor containment strategy has been supported very recently by mathematical analyses [18]. In brief, the authors show that the promotion of ecological competition between resistant- and sensitive-to-drug tumor cells via the administration of doses below the maximum tolerable delays the arrival of tumor resistances, thus prolonging patient survival [18].

## Games

Game theory is a branch of applied mathematics that analyzes bilateral or multilateral interactions between individuals to predict collective behaviors, usually in the field of political and economic science. This mathematical tool has also been applied to analyze biological problems, and lately to explore the complexity of cancer. The hawk-dove game [19], the prisoner's dilemma [20], coordination games [21], and multiplayer public good games such as the volunteer's dilemma [22], for example, are different theoretical scenarios that have been applied to cancer analysis in recent years.

The hawk-dove game explores the dynamics generated between two individuals (cancer cells) belonging to the same group (cancer) when they play either aggressively (hawk) or passively (dove). Each cell plays one of these roles depending on the opponent's type because they do not recognize their own type [23]. The game seeks to identify evolutionarily stable strategies (ESS) in the group studied. An ESS is a strategy adopted by all the components of a community in response to specific environmental conditionings by which every element of the group maximizes its payoff when the other elements adopt the same strategy [24]. This collective situation is called a symmetric equilibrium (Nash equilibrium). It is impermeable by definition and cannot be modified by the actions of external individuals. The payoff is an increase in fitness, i.e. the capacity to increase the cell reproduction rate, a direct measure of tumor aggressiveness. In the game, cells may cooperate or fight, but they always behave in the context of ESS within the group. The context includes the securing of a resource on one hand, and the payment of the cost for securing it on the other. Using this game, some authors [19,25] have proposed encounters between two different epithelial phenotypes in prostate cancer in which survival rests on their dependence on or independence of the microenvironment. In pathological terms, the game includes stromogenic low-grade versus non-stromogenic high-grade prostate adenocarcinomas. The authors conclude that a hawk-dove game underlines the importance of the microenvironment in prostate cancer prognosis and evolution.

The prisoner's dilemma, another well-known game, has been extensively applied in political science and economics, and latterly also in cancer[20]. The game poses a situation in which two prisoners may choose to cooperate or not, even though they know that the cooperation is advantageous for both. Concerning cancer, imagine the interactions between two cell populations to get a payoff useful for both cells. Group A is composed of non-tumor cells, and group B of tumor cells. Very importantly, A cells do not know what the attitude of B cells in the game will be, and vice versa, but they both know that cooperating will provide the maximum payoff. Also, A and B cells know that if neither of them cooperates they will get only a minimal payoff. Finally, both cell types know that the cooperation of only one of them (for example, A) will provide a payoff for the other (for example, B). Since the prisoner's dilemma is a paradigmatic game to analyze interactions between selfish individuals, the probable final result will be non-cooperation, with a minimal benefit for both players. However, the result of this game may be different in biology in specific situations quite common in cancer, e.g. metastasis. Imagine a colon adenocarcinoma metastasizing to the liver. In this case hepatocytes will cooperate by default because they are basally programmed to do so; however, as a result of any deprogramming somatic mutation, metastatic colon cancer cells will not. In this context, the cooperation of hepatocytes will provide a payoff for metastatic colon cancer cells, which will increase tumor cell fitness and, hence, cancer aggressiveness.

Coordination games analyze methods to incentivize uniformity in a group in such a way that any individual deviation from that uniformity will lead to decreasing payoffs for the whole group. There are several degrees of astringency to this rule. For example, pure coordination games necessarily require absolute positive uniformity in the group to get the best collective payoff, but an absolute negative uniformity will result in a smaller payoff, while divergencies in uniformity between individuals within the group will produce a payoff of zero. The choosing-sides game, proposes an all-or-nothing reward for individuals, e.g. if and only if all car drivers choose to drive on the same side of the road will the payoff be maximum, and any other possible alternative will provide a benefit of zero. A less astringent variant of this type of games is the so-called stag hunt game. Here, non-coordination between individuals provides low payoffs whereas coordination provides high payoffs. Using a modification

of the Lotka-Volterra model of competition, coordination games have been proposed to improve current cancer treatments by hypothesizing on a comparison between two different therapeutic strategies: one that increases tumor cell deaths and another that increases tumor cell mutation rates [21].

The best example of *N*-player public good games is the so-called volunteer's dilemma, which models social dilemmas not only in communities of unicellular organisms (bacteria, amebae, etc.) and vertebrates [26,27] but also in cancer cell communities [28]. The volunteer's dilemma arises when some individuals in a community are needed to produce a public good. Volunteering has a cost that is paid only by volunteers while the rest share in the benefit by doing nothing. The absence of the public good is also costly for the community, so a stable equilibrium between collaborators and free riders appears while the number of individuals in the community remains unchanged. The dilemma arises when the number of individuals in the group changes, because the social benefit decreases as group membership increases as a result of a proportionally smaller possibility of volunteering. This evidence has led Archetti [26] to define the optimal size of a group in social dilemmas as that which maximizes the possibility of producing the public good. A typical scenario to explain the volunteer's dilemma is a group of antelopes in the African savanna under threat from predators. Here, the benefit for the antelopes is to survive and the cost for the volunteer is to take the risk of being hunted first. The dilemma for an individual in this context lies in deciding to announce the imminent risk to the group. This is a choice that will put the individual animal at risk or, if it decides to cheat, will put the whole group at risk.

Free riders, however, can be beneficial for the group under specific circumstances. In other words, a combination between collaborators and free riders is the perfect situation for group survival against a common enemy. Such social dilemmas have been applied to analyze interactions between tumor cells and immune system cells considering tumor cells as antelopes and immune cells as predators[28]. Under these experimental conditions, using this game, the authors elegantly demonstrate that the presence of free riders helps the tumor overcome the effects of the immune system [28], an interesting and paradoxical finding that once more connects cancer with ecological principles, thus closing the link between ecology, games, and cancer, which was the intention of this narrative.

## Conclusions

Current studies are largely dominated by the identify-

ing of targetable genomic signatures and by precision medicine. Pathologists and oncologists should consider incorporating a broader perspective of analysis to strengthen knowledge of cancer and open up new opportunities for therapy. This brief overview highlights the importance of considering the sociological side of cancer as a potential method of analysis for understanding why tumors behave as they do.

## References

1   Reynolds BA, Oli MW, Oli MK. Eco-oncology: Applying ecological principles to understand and manage cancer. Ecol Evol 2020;10:8538-8553. https://doi.org/10.1001/ece3.6590

2   Tabassum DP, Polyak K. Tumorigenesis: it takes a village. Nat Rev Cancer 2015;15:473-483. https://doi.org/10.1038/nrc3971

3   Axelrod R, Pienta KJ. Cancer as a social dysfunction. Why cancer research needs new thinking. Mol Cancer Res 2018;16:1346-1347. https://doi.org/10.1158/1541-7786.MCR-18-0013

4   Gatenby RA. A change of strategy in the war on cancer. Nature 2009;459:508-509. https://doi.org/10.1038/459508a

5   Thomas F, Roche B, Giraudeau M, et al. The interface between ecology, evolution, and cancer: More than even a relevant research direction for both oncologists and ecologists. Evol Appl 2020;13:1545-1549. https://doi.org/10.1111/eva.13031

6   Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Eng J Med 2012;366:883-892. https://doi.org/10.1056/NEJMoa1113205

7   Greenman CD, Pleasance ED, Newman S, et al. Estimation of rearrangement phylogeny for cancer genomes. Genome Res 2012;22:346-361. https://doi.org/10.1101/gr.118414.110

8   Mitchell TJ, Turajlic S, Rowan A, et al. Timing the landmark events in the evolution of clear cell renal cell cancer: TRACERx Renal. Cell 2018;173:611-623. https://doi.org/10.1016/j.cell.2018.02.020

9   Davis A, Gao R, Navin N. Tumor evolution: linear, branching, neutral or punctuated? Biochim Biophys Acta 2017;1867:151-161. https://doi.org/10.1016/j.bbcan.2017.01.003

10  Ling S, Hu Z, Yang Z, et al. Extremely high genetic diversity in a single tumor points to prevalence on non-Darwinian cell evolution. PNAS 2015;112:E6496-E6505. https://doi.org/10.1073/pnas.1519556112

11  Turajlic, S, Xu H, Litchfield K, et al. Deterministic evolutionary trajectories influence primary tumor growth: TRACERx Renal. Cell 2018;173:595-610. https://doi.org/10.1016/j.cell.2018.03.043

12  De la Fuente IM, Cortes JM, Valero E, et al. On the dynamics of the adenylate energy system: homeorhesis vs homeostasis. PLoS One 2014;9:e108676. https://doi.org/10.1371/journal.pone.0108676

13  Hansen E, Read AF. Cancer therapy: Attempt cure or manage drug resistance? Evol Appl 2020;13:1660-1672. https://doi.org/10.1111/eva.12994

14  Parrondo JM, Harmer GP, Abbott D. New paradoxical games based on Brownian ratchets. Phys Rev Lett 2000;85:5226-5229. https://doi.org/10.1103/PhysRevLett.85.5226

15  Cheong KH, Koh JM, Jones MC. Paradoxical survival: Examining the Parrondo effect across biology. Bioessays 2019;41:e1900027. https://doi.org/10.1002/bies.201900027

16  Capp JP, Nedelcu AM, Dujon AM, et al. Does cancer biology rely on Parrondo's principles? Cancers (Basel) 2021;13:2197. https://doi.org/10.3390/cancers13092197

17  Kim Y, Das T, Tian H. et al. Sweat but no gain: Inhibiting proliferation of multidrug resistant cancer cells with "ersatzdroges". Int J Cancer 2015;136:E188-E196. https://doi.org/10.1002/ijc.29158

18  Viossat Y, Noble RA theoretical analysis of tumour containment. Nat Ecol Evol 2021;5:826-835. https://doi.org/10.1038/s41559-021-01428-w

19  Basanta D, Scott JG, Fishman MN, et al. Investigating prostate cancer tumour-stroma interactions: clinical and biological insights from an evolutionary game. Br J Cancer 2012;106:174-181; https://doi.org/10.1038/bjc.2011.517

20  West J, Hasnain Z, Mason J, et al. The prisoner's dilemma as a cancer model. Converg Sci Phys Oncol 2016;2:035002. https://doi.org/10.1088/2057-1739/2/3/035002

21  Bayer P, Gatenby RA, McDonald PH, et al. Coordination games in cancer. PLoS One 2022;17:e0261578. https://doi.org/10.1371/journal.pone.0261578

22  Renton J, Page KM. Cooperative success in epithelial public good games. J Theor Biol 2021;528:110838. https://doi.org/10.1016/j.jtbi.2021.110828

23  Inarra E, Laruelle A. Artificial distinction and real discrimination. J Theor Biol 2012;305:110-117. https://doi.org/10.1016/j.jtbi.2012.03.034

24  Maynard Smith J, Price G. The logic of animal conflict. Nature 1973;246:15-18; https://doi.org/10.1038/246015a0

25  Anderson AR, Hassanein M, Branch KM, et al. Microenvironmental independence associated with tumor progression. Cancer Res 2009;69:8797-8806. https://doi.org/10.1158/0008-5472.CAN-09-0437

26  Archetti M. The volunteer's dilemma and the optimal size of a social group. J Theor Biol 2009;261:475-480. https://doi.org/10.1016/j.jtbi.2009.08.018

27  Archetti M. Cooperation as a volunteer's dilemma and the strategy of conflict in public good games. J Evol Biol 2009;22:2192-200. https://doi.org/10.1111/j.1420-9101.2009.01835.x

28  Morsky B, Vural DC. Cheater-altruist synergy in public good games. J Theor Biol 2018;454:231-239. https://doi.org/10.1016/j.jtbi.2018.06.012