Can Game Theory Explain Invasive Tumor Metabolism?

By Mike Martin

Game theory, the discipline behind the Oscar-winning film *A Beautiful Mind* and the science that predicts strategies and payoffs in competitive scenarios, may explain how invasive cancer cells gain the upper hand in certain metabolic scenarios.

For a report published in the December 2008 issue of *Cell Proliferation*, German researchers Andreas Deutsch, Ph.D., and Haralambos Hatzikirou, Ph.D., from the Dresden University of Technology, and colleagues studied how tumor cells compete in the survival game.

Applying the tools of game theory to low-grade glioma growth, Deutsch and his team found that in a tumor populated by glycolytic cells, invasive cells have a better chance of emerging. They conclude that the findings may explain invasive growth under otherwise nonmalignant circumstances, and they suggest anti-invasive therapeutics.

"To the best of our knowledge, ours is the first attempt to use game theory to analyze the interplay of different tumor cell phenotypes with respect to tumor invasion," said coauthor David Basanta, Ph.D., a postdoctoral research fellow at the H. Lee Moffitt Cancer Center's mathematical oncology program in Tampa, Fla.

Mathematical Oncology

The game theory approach to cancer is based on the idea that spontaneous mutations give rise to tumors, but not in a vacuum. Nature is nurtured at the cellular level, and to find out how, cancer researchers have focused on the tumor microenvironment. A key assumption about the tumor microenvironment hails from evolutionary biology: The fitness of a cell with a characteristic phenotype depends on its interaction with other cells that have different phenotypes.

"In the evolutionary sense, only traits that allow successful adaptations survive," said Phillip Manno, M.D., chief of clinical oncology and hematology at the Nevada Cancer Institute in Las Vegas. "This idea can certainly be applied to cancer, in which cells acquire a needed phenotype to survive." With the right mathematical approach, researchers can frame intercellular interactions that lead to phenotype acquisitions as survival games.

Coming from a long tradition in sociology, economics, and more recently, biology, "game theory has been used successfully to study the evolutionary dynamics of populations made of different phenotypes in traditional ecosystems," said Basanta. "We believe it can be used to study the evolutionary trajectories of cancer."

Some researchers consider carcinogenesis itself an evolutionary trajectory. In almost stepwise progression, cancer cells evolve by acquiring different phenotypes, including the ability to trigger blood vessel growth, invade surrounding tissue, metastasize, and grow autonomously.

As these phenotypes evolve, survival strategies come into play that British geneticists Ian Tomlinson, Ph.D., and Walter Bodmer, Ph.D., first cast in a game theoretic framework for a seminal 1997 article in the *European Journal of Cancer*.

Studying tumor cells that produce a cytotoxin harmful to other tumor cells, Tomlinson and Bodmer likened tumors to cell "populations" that engage in biochemically mediated "social interactions," some of which favor individuals at the population's expense. Their discovery—that "some tumor cells adopt genetically determined strategies to boost their own replication at the expense of other tumor cells"—suggested an intriguing hypothesis with therapeutic implications: "Strategies that retard the growth of the tumor can be selected and tumor regression is theoretically possible."

Since then, a body of literature has developed that borrows heavily from the work of game theory pioneers John von Neumann; Oskar Morgenstern; and the beautiful mind himself, Princeton mathematician and Nobel laureate John Forbes Nash. Viewing carcinogenesis as an evolution, game theory predicts which phenotypes will emerge and under what conditions they will either die or thrive.

"Carcinogenesis can seem deterministic in this sense, but the overall picture is actually rather stochastic," said the Nevada Cancer Institute's Manno. That element of randomness or chance, he said, adds to the complexity of cancer but also makes game theory an apropos and practical modeling tool. He says that applications such as those described in the report—which postulate that complex behavior is based on simple systems and that cells share inherent rules that depend on the states of neighboring cells—give him, as a clinical oncologist, insight into the biology of cancer and its possible interactions with treatment interventions.

Payoff table that represents the change in fitness of a tumor cell with a given phenotype interacting with another cell

Phenotype	AG	INV	GLY
AG	½	1 – c	½ + n – k
INV	1	1 – c/2	1 – k
GLY	½ – n	1 – c	½ – k

Source: *Cell Proliferation*, Dec. 2008; 41(6): 980–7.

Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion.

Basanta D., Simon M., Hatzikirou H., Deutsch A.

Survival Savvy

In their study, the researchers started with a spontaneous mutation, which Deutsch sees as conferring an evolutionary advantage. In a process known as the Warburg effect, the mutation lets both malignant and nonmalignant tumor cells switch from the aerobic Krebs cycle to anaerobic glycolysis for energy production, acquiring a survival-savvy phenotype in the process.

Glycolysis and the Krebs cycle are cellular metabolic pathways that produce high-energy molecules such as ATP and NADH from metabolites such as glucose and citrate. Though glycolysis is less efficient than the Krebs cycle, producing 75% fewer NADH molecules, it can operate in oxygen-starved environments where "demands by a growing number of tumor cells are no longer met by the vascular supply of the tumor," said Deutsch, who directs the department of innovative methods in computing at the Dresden University's High-Performance Computing Center.

Building on earlier research from Moffitt diagnostic imaging specialist Robert Gatenby, M.D., which showed glycolysis routinely preceding invasiveness in certain cancers, Deutsch and his team studied nine different game theoretic scenarios involving glycolytic, invasive, and autonomously growing tumors.

"We found that the invasive phenotype is more likely to evolve after the appearance of the glycolytic phenotype," Deutsch said. "The result suggests that therapies which increase the fitness cost of switching to anaerobic glycolysis—such as improving tissue oxygenation—might decrease the emergence of more invasive phenotypes."

Costs and Payoffs

Making "no assumptions as to what genetic changes are necessary for mutations to occur," the Deutsch–Basanta team built a payoff table—a standard game theory tool that produces mathematical equations describing the costs and benefits of hypothetical strategies. Their table used symbols for three different phenotypes: autonomous growth (AG); anaerobic glycolysis (GLY); and motile invasiveness (INV) (*see* graphic).

Using fitness cost variables k and n, the payoff table represents how the fitness of a tumor cell with a given phenotype changes on interactions with other cells in the tumor microenvironment. Switching to less-efficient glycolytic (GLY) metabolism incurs fitness cost k. Variable n represents the phenotype-dependent fitness of a low-oxygen environment: Nonglycolytic cells lose, whereas glycolytic cells gain.

Under ideal circumstances, a tumor cell shares nutrients and space with no other cells and achieves maximum fitness—the so-called base payoff of 1. An example from the table is the fitness payoff for an AG cell interacting with another AG cell: The payoff is 1/2, because the cells incur no costs beyond splitting available resources.

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Studying a hypothetical tumor in which all three phenotypes—AG, GLY, and INV—coexist at the same fitness levels in equilibrium, the researchers used a string of complicated equations that yielded a simple result: $p(\text{INV}) = 1 - k/n$, where $p(\text{INV})$ is the proportion of invasive cells in the tumor. The equation shows that, for low values of k and/or high values of n—in other words, when switching to less efficient glycolysis isn't costly compared to the benefits gained—INV cells predominate, displacing the other phenotypes from the tumor.

"This means that conditions favoring glycolysis also favor invasiveness," Hatzikirou explained. "The low-oxygen microenvironment selects for both glycolytic cells and motile cells that can move away."

Noting that he was "particularly fascinated" with the three-phenotype scenario, "which is realistic of common tumors exhibiting a heterogeneous mass," Manno said that the authors "succeed in their objectives in a simplistic sense. Malignant cells have survival characteristics that can overcome many different environments as long as the net gains can be justified."

Likening the three phenotypes to three prisoners on the verge of betraying each other to gain their own freedom in the famous "Prisoner's Dilemma" game, Smith College game theorist Jim Miller, Ph.D., agrees that "using evolutionary game theory to illustrate invading cells is a sound approach." An associate professor of economics, Miller applies game theory to litigation, perjury, lotteries, and even Greek mythology. After reviewing the Deutsch-Hatzikirou-Basanta study, he compared the INV phenotype to the selfish prisoner; the GLY phenotype to the altruistic prisoner; and the AG phenotype to the prisoner who can be either selfish or altruistic, depending on the circumstances.

Andreas Deutsch, M.D.

"Like the invasive phenotype, selfish mutants can arise in an altruistic population, destabilizing it," Miller said from his office in Northampton, Mass. "Raise the cost of being selfish and you lower the proportion of selfish prisoners and stabilize the population." Thus, raising the "cost" to the cells of becoming invasive should halt cancer progression.

Clinical Implications?

Benign, low-grade gliomas—glial cell tumors of the central nervous system—sometimes exhibit a puzzlingly malignant behavior: They invade surrounding tissues, but not always and not inevitably—a circumstance that makes glioma a reasonable model for the study of invasion and malignancy.

The Deutsch-Hatzikirou-Basanta study predicts that a low-grade glioma will invade the surrounding brain parenchyma when GLY cells predominate. Metastasis—which studies suggest occurs in more than 50% of gliomas—shouldn't be far behind. "Motility

is a requirement for malignancy, so the emergence of invasive phenotypes should correlate with the tumor becoming metastatic," Basanta said.

These predictions have clinical implications, which Basanta discussed in a 2008 report for the *European Physical Journal*. "Low oxygenation favors invasion," he said. "Increasing the oxygenation of the tumor before glycolytic cells have the opportunity to spread would increase the cost of glycolysis, which might hinder the emergence of motile cells and thus delay or potentially even prevent invasion and metastasis."

But just how well increasing tumor oxygenation would work in practice Manno said he isn't sure, nor whether it would prevent, slow, or otherwise interfere with invasion and metastasis.

Game theory applied to carcinogenesis has its challenges. Alexander Anderson, Ph.D., who codirects Moffitt's mathematical oncology program, said that game theory "is certainly a useful tool to investigate cancer. But it does not give many dynamics, such as how different phenotypes compete for space."

Acknowledging that "lack of spatial considerations is probably the most significant omission in our approach," Dresden's Deutsch said he eventually wants to consider "a larger number of phenotypes" in three dimensions, asking how the cost of motility, for instance, increases as a growing tumor runs out of space.

Spatial considerations are especially important with a tumor such as glioma in a confined area such as the brain, said Anderson. "The heterogeneous distributions of gray and white matter impact how the tumor invades," he said, noting that pathologist Kristin Swanson, M.D., of the University of Washington–Seattle "has shown that the brain structure to some extent dictates how a glioma grows."

That said, Anderson added that he "likes the paper overall, especially its simplicity. I think the results are applicable to solid tumors in general, which highlights the strength of the game theory approach."

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