**PHYSICS AND CARCINOGENESIS**

Does Homeostatic Pressure Explain Tumor Growth?

By Mike Martin

To the much-studied genetic and biochemical forces that govern cell growth, dysplasia, and metastasis, a burgeoning science—call it mechanical biology—is adding forces that might seem more applicable to airliners and skyscrapers. Shear, friction, stress, tension, and viscosity also play a role in oncogenesis, according to researchers exploring this interface between biology and physics.

“Tumor growth is a multistage process that requires cells to pass through multiple checkpoints,” said Jacques Prost, Ph.D., of the Curie Institute in Paris, a leader in the physical sciences research department where Pierre and Marie Curie discovered radium and Paul Langevin discovered sonar. “Mechanical forces are at work, hence the necessity of investigating their importance.”

In a new report, Prost and his colleagues propose a mathematical model, based on existing clinical and laboratory data, that explains how a mechanical force that they call homeostatic pressure affects tumor growth and metastasis. Writing in the American Institute of Physics *HFSP Journal*, the physicists argue that analyzing cancer strictly on the basis of DNA abnormalities or chemical on–off switches cannot fully account for clinical and experimental data. The authors claim that their approach could lead to “a quantitative, experimentally accessible measure for the metastatic potential of early malignant growths.”

“Genes do not move matter—physical mechanisms and processes do,” said Gabor Forgacs, Ph.D., a professor of biological physics and biomedical engineering at the University of Missouri, Columbia. Summing up the argument for investigating the physics of carcinogenesis, Forgacs said the Prost group’s analysis “illustrates how simple physical concepts like pressure can be applied to the ultimate intricate biological system: the tumor.”

**Homeostatic Pressure**

Distinct from osmotic or hydrostatic pressure, homeostatic pressure results from the mechanical stress that cells experience as they expand against surrounding tissues. According to Prost, “this pressure reaches homeostasis, or equilibrium, when cell division balances cell death.”

To illustrate, the Curie group pictures a chamber permeable to water, nutrients, oxygen, and growth factors within which growing cells expand against a spring-loaded piston. As they proliferate, the cells compress the piston until a steady state results that halts further growth under normal conditions. At this homeostatic point, with biochemical and genetic factors otherwise constant, rising pressure alone causes cell division to balance cell death and growth ceases.

The authors characterize homeostatic pressure as “an important property for describing the competition” between a tumor and the normal tissue surrounding it. To penetrate that tissue and metastasize, the group claims, malignant cells must reach a threshold—the critical size. Otherwise, they will shrink and die. The authors argue that because mechanical pressure can prevent tumors from reaching critical size, increasing the mechanical strength of surrounding tissue, or stroma—in effect blocking the tumor’s ability to expand—may represent a viable way to treat some cancers.

To describe their theory mathematically, Prost and his team used a continuity equation, with terms for the probability of cell division ($D$), apoptosis ($A$), and homeostatic pressure ($HP$):

$$D_{tumor} - A_{tumor} = HP_{tumor} - HP_{stroma}$$

According to the equation, tumor cell growth will outpace tumor cell death so long as the tumor’s homeostatic pressure exceeds that of the surrounding stroma.

**Hard Data**

To back their mathematical variables with real numbers, Prost and his group analyzed data from nearly 40 experiments and studies, most from the last 10 years. Cellular viscosity and surface tension measurements, for instance, came from work by Forgacs and Rutgers University molecular biologist Ramsey Foty, Ph.D. A study published by University of California–Santa Barbara statistical physicist Boris Shraiman, Ph.D., provided not only raw data but also a model approach.

To arrive at their own measure of a tumor’s propensity to reach critical size, the Curie group modified a mathematical construct developed by the Dutch physicist Nico Van Kampen, Ph.D., called a “splitting probability”—the probability that a cell will either reach a certain size or die. Implanting the liver or lungs of a lab mouse with a few hundred thousand cancerous cells illustrates this concept. “After about 3 weeks, most of the cells die,” explained Curie biologist Thomas Risler, Ph.D. Only a few cells reach the critical size threshold, large enough to grow into clinically relevant tumors. “For smaller than the critical size, the probability that a macroscopic tumor will grow from microscopic cells is very small,” Risler said.
Marshaling other mathematical techniques such as Monte Carlo simulation and the Gillespie algorithm, the group generated graphics-rich computer models that correspond to data from previous laboratory experiments. Prost points, for instance, to a 1997 study, in which Novartis Corp. computational biologist Gabriel Helmlinger, Ph.D., and Rakesh Jain, Ph.D., who directs Harvard University’s Edwin Steele molecular oncology lab, found that tumors growing in agarose gels proliferate until the pressure exerted by the gel reaches 45–120 mm Hg. “Their experiment gives an estimate of the homeostatic pressure as defined in our paper,” Prost said.

The idea of applying spatial and physical parameters to tumor growth came to Prost’s team—which includes Risler as well as two other physical biologists, Jean-Francois Joanny, Ph.D., and Markus Basan, Ph.D., along with pathologist Xavier Sastre-Garau, M.D., Ph.D.—during a workshop.

“On several occasions, it was mentioned that tumors were arising at boundaries between tissues or at heterogeneous places where different tissues meet, like hair roots,” Prost explained. The discussion reminded him of a concept familiar to physicists called heterogeneous nucleation. Defined as the “localized budding of a distinct liquid, gas, or solid phase,” heterogeneous nucleation occurs at the interface of two different thermodynamic phases—where a liquid meets a solid, for instance, or where a solid meets a gas. At these interfaces, conditions favor budding—think of air bubbles forming in a drink along a straw or of water vapor turning into rain along a seeding of granular cloud pellets. A biological version of budding suggests that tumors start out as tissue “buds” in preferred locations such as folds, membranes, and interfaces where different tissues meet. Lower homeostatic pressure, Prost and his team surmise, makes these sites preferable to areas where the tissue is denser, stiffer, thicker, or harder.

Countering the enthusiasm of the physical biologists, other researchers caution that mechanical forces cannot account for everything going on during carcinogenesis. Edna Cukierman, Ph.D., a cell biologist at Fox Chase Cancer Center in Philadelphia, said that in the Curie group’s study, “the authors tend to oversimplify the biology in order to establish mathematical parameters and physical variables.” She added, however, that “this is a problem they seem to understand and acknowledge.”

**Not Convinced**

Oncologist Clay Anderson, M.D., echoed Cukierman’s concern. He’s not convinced that \( A \) and \( D \)—the variables for apoptosis and cell division, respectively—adequately account for myriad but necessary genetic and biochemical factors.

Instead, Anderson, an associate professor of clinical medicine at the University of Missouri, worries that the Curie group’s hypothesis “discounts a great deal of evidence that metastasis is a genetically driven phenomenon.” And though he’s impressed that their report presents several testable hypotheses, he said that Prost and his colleagues “need to better show why this explanation works.”

Prost said he’s heard “criticisms that reject our approach for not having explicit references to genetic mechanisms” before. Variables in the continuity equation that describe cell division and death do account for genetic influences, he said. But he acknowledged that those variables have yet to be measured and that their clinical effects remain unknown.

But even if the variables are measured and even if the math proves correct, Forgacs says, homeostatic pressure has limited application and may play a role only in early-stage tumors. Advanced malignancies use secreted enzymes called matrix metalloproteinases to degrade the extracellular matrix, “eating through it” to expand. “This enzyme-driven process invalidates the tumor’s earlier dependence on interfacial tension to grow between itself and the extracellular matrix,” Forgacs said.

The Curie group is just one of a growing number of laboratories studying the effects of mechanical forces on tumors. And homeostatic pressure is just one of the hypotheses put forward.

At the University of California, San Francisco, for instance, associate professor Valerie Weaver, Ph.D., is investigating the role of tissue architecture in the pathogenesis of therapy-resistant breast cancers. The Curie team’s report, Weaver said, “discusses yet another important and interesting aspect of tumor growth—tension between boundaries—that has not been addressed in depth and could explain some behaviors in metastatic tissues.”

Interboundary tension is critical to a burgeoning subdiscipline of mechanical biology called cell rheology, the study of flow as it applies to cells and soft tissues. “Tumors display physical characteristics that deform their surroundings and hence their ability to move in those surroundings,” said Weaver who is director of the Center for Bioengineering and Tissue Regeneration at UCSF.

“For that reason, tumor development is as much a mechanical process as it is chemical or genetic.”

In a sign that such approaches are beginning to win wider recognition, the National Cancer Institute recently held a series of workshops on how physics—energy flows, gradients, mechanics, and thermodynamics—affects cancer. NCI has also announced that some of its new funds from the economic stimulus legislation will go to create a network of physical science–oncology centers, suggesting a growing recognition of the new field. Physical forces in biological systems, Weaver said, “need to be explored in much greater depth.”

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