Physics of Cancer Takes Shape

A concept in condensed-matter physics called jamming provides a possible prognostic tool for cancer.

By **Liesbeth M. C. Janssen**

Cancer is a highly complex, multifaceted disease that accounts for nearly one in six deaths worldwide. More than 90% of cancer deaths are due to metastasis—the process by which cancer cells escape from the primary tumor, spread through the body, and seed a secondary tumor in a distant organ or tissue. Given these sobering numbers, it should come as no surprise that researchers consider a better mechanistic understanding of metastasis to be of eminent importance in the fight against cancer. What is perhaps more of a surprise is that a key role in this fight may be played by condensed-matter physics. Pablo Gottheil of Leipzig University in Germany and colleagues have illustrated why this is the case by showing that concepts of soft condensed matter—in particular, the physics of disordered systems—can improve the long-term metastatic risk assessment of breast-cancer patients [**1**].

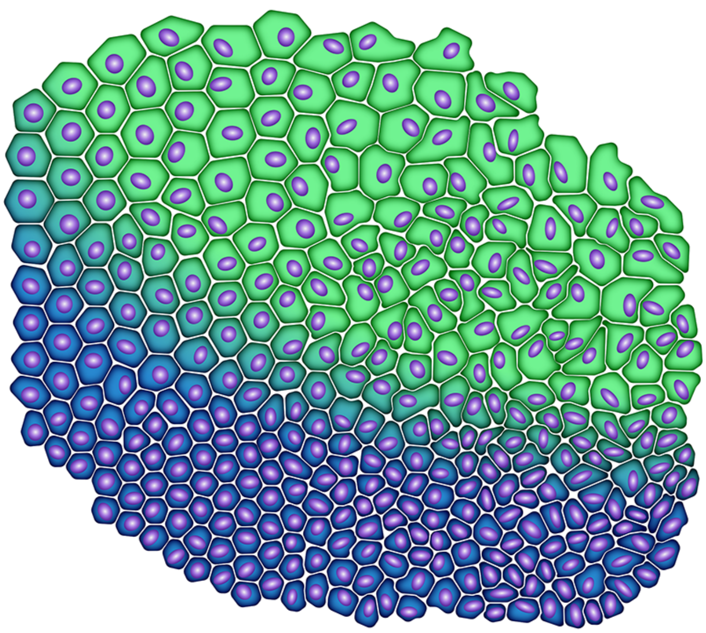

Figure 1: Gottheil and colleagues present a state diagram that links the morphology of cancer cells to their motility [**1**]. Cell nuclei are depicted in purple, and cells are color coded using a heat map, where blue and green indicate low and high motility, respectively. Small, roundish cells with roundish nuclei (bottom left) have low motility, whereas large, elongated cells with elongated nuclei (top right) have high motility.
Credit: P. Gottheil *et al.* [**1**]

Physicists have long contributed to cancer research by developing, for example, advanced imaging tools. But it is only in the past decade or so that the development of the disease itself, especially the onset of metastasis, has been recognized as a bona fide physics problem. The basic idea is simple: no matter how complex the genetic and biochemical signatures of cancer are, all cancer cells must ultimately obey the laws of physics when they move, deform, and migrate through the body. In the past few years, this uniquely physical approach—dubbed the physics of cancer—has emerged as a promising paradigm to provide insights into key aspects of cancer progression.

Conventionally, the physics of disordered systems deals with the behavior of inanimate materials such as granules, complex fluids, and glasses. A special property of these materials is that they can rapidly switch from liquid-like to solid-like behavior while preserving their disordered structure—an intriguing phenomenon known as jamming [**2**]. About a decade ago, groundbreaking work established that living cells also exploit physical jamming in densely packed cell layers and tissues [**3**]. Indeed, akin to how a pile of sand can flow through your fingers at one moment and be part of a solid sandcastle the next, deformable cells can switch between mobile and stationary states without compromising the structural integrity of the tissue. Even more enthralling is the growing realization that such cellular jamming and unjamming transitions might have important biological functions in both health and disease [**4**, **5**].

The relevance of unjamming in cancer is rooted in a simple physical notion: to metastasize, cancer cells must move. Enhanced cell motility in cancerous tissue can be triggered by a multitude of signals, including genetic and environmental cues [**6**]. However, increasing evidence suggests that an emergent unjamming transition is also at play in primary tumors. But how can cells unjam in a tightly packed solid tumor, and to what extent does unjamming truly matter for the final metastatic outcome? Both of these questions have now been addressed by Gottheil and colleagues in an innovative study that combines physics-based principles with clinical cancer-patient data.

To answer the first question, the researchers build upon the discovery in the past decade that the shape of cells can be a remarkably good informant on the degree of jamming in dense cell layers [**7**, **8**]. Explicitly, elongated cells tend to be more mobile than roundish ones because they can more easily squeeze between—and exchange positions with—their neighbors. But cell shape alone is not a sufficient structural order parameter for jamming and unjamming in solid tumors [**1**, **9**]. Gottheil and colleagues use patient-derived breast-cancer cells to show that the nucleus of the cell should also be considered. A physically intuitive reasoning for this finding is that the nucleus is a relatively large and stiff object that can mechanically hamper a cell's ability to move through a dense environment.

The researchers combine knowledge of both the cellular and nuclear shapes into a new order parameter called CeNuS. They then propose a link between this simple static information and the emergent cellular motility—and hence the degree of unjamming—in primary breast-cancer cells. This morphodynamic link also forms the basis for a state diagram of cancer-cell unjamming (Fig. **1**), which can be used to readily estimate the status of unjamming for a given tissue sample from a patient.

To explore whether a greater degree of unjamming also correlates with greater metastatic risk, Gottheil and colleagues take another major step by performing a retrospective study on clinical data of 1380 breast-cancer patients. Remarkably, the researchers find that an increase in predicted unjamming significantly correlates with the development of distant metastases that might even occur a decade later. This result also implies that the state of cellular unjamming—as assessed via CeNuS—can serve as a complementary prognostic biomarker for cancer. Indeed, when combined with conventional risk-assessment criteria, the inclusion of physical unjamming boosts the prognosis accuracy for metastasis from 66.8% to 71.3%. This improvement corresponds to a 26% increase in prognostic information when compared to the use of established parameters alone. Overall, these findings suggest that the emergent physics of disordered condensed matter could play a vital part in metastasis.

Aside from the relevance to cancer, let us recall that, more generally, jamming and related glassy phenomena rely on subtle structural changes that act to either liquefy or solidify an amorphous material. On the one hand, the absence of any major structural changes renders understanding these transitions one of the most complex problems in classical physics. But on the other hand, it offers wonderful practical convenience [**10**]: with only minimal particle rearrangements or deformations, a system can easily alter its collective properties. It is plausible that living cells and tissues have cleverly managed to exploit this behavior by evolving toward a state that remains close to a jamming or unjamming threshold, such that they can efficiently switch between high motility and dormancy. In the coming years, we can therefore expect the physics of disordered systems to gain increasingly more recognition in the biological sciences.

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