How Cancer Cells Go Awry: The Role of Mechanobiology in Cancer Research

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Abstract: Cancer is the second leading cause of death in the US and is projected to overtake cardiovascular disease as the leading cause of death in the next few years. Few patients die from primary tumors, but once a tumor has spread to other parts of the body (a process called metastasis), it becomes much more difficult to treat. 90% of cancer deaths are due to metastasis. The exact mechanisms by which tumors form, grow, and spread is not clear, however significant attention has been paid to the role of genetic mutations within cells that drive uncontrolled growth. While genetics and gene mutations are clearly drivers of cancer, it is now known that they are not the only key players. The chemical and physical environment surrounding tumor cells also contributes to malignancy and metastasis. Numerous tumors are diagnosed based on the physical properties of the tumor: as an example, changes in tissue stiffness and density are markers of tumor formation detectable by palpation and medical imaging. Notably, changes in tissue stiffness and density have been shown to enhance tumor progression. As such, research is now not only focused on the causes and treatments of genetic mutations and molecular changes within the cell, but also on the physical changes occurring in the tissue and cells. This requires a new arsenal of tools aimed at characterizing and controlling the physical properties of cells and tissue. Engineers have made significant strides in developing the tools and models necessary to understand and attack cancer.

Overview of Cancer and Metastasis

Tumors are generally thought to form from one initial rogue cell that undergoes genetic changes that results in its uncontrolled growth and proliferation[1]. As this proliferation occurs, the tumor is

considered benign as long as the cell mass remains resident within the tissue in which it has formed. In this case, it is not considered cancer, but can sometimes be dangerous if its size is compressing nerves, arteries or other tissues. If, however, the cells invade into the surrounding tissue, it is then considered cancerous. The cells can spread to surrounding tissues, often traveling through the bloodstream and/or lymph systems to move to other organs in the body. As such, there is immense interest in determining 1. What triggers the initiating steps that lead to uncontrolled proliferation, 2. What are the determinants of invasion?, 3. How to prevent the spread of tumor cells in the lymph system and blood stream.

Staging of cancer is done to categorize the extent of the spread of the tumor in a common clinical language that all physicians can understand and utilize to establish a prognosis, determine a course of action, and determine the fit for a clinical trial. Staging is based on several key factors including the location and size of the primary tumor, whether the tumor has spread to the lymph nodes, and whether the tumor has spread to other distant areas of the body. The TNM staging system is based on categorizing the size and extent of the primary tumor (T), the spread to regional lymph nodes (N) and the presence of secondary metastatic tumor sites in other organs (M). Each of these (T, N and M) is then used to determine the numerical stage of the cancer (I-IV). Staging is cancer-type specific, and exact stage depends on the type of tumor and its location. Stage I is indicative of a cancer that is the last advanced and has the best prognosis, whereas Stage IV indicates that the cancer has spread to other areas of the body and is typically much more difficult to treat. In general, if a cancer is identified and treated before it has spread, the outcomes are favorable. For this reason, significant attention has been paid stopping cancer progression before the cells metastasize.

Mechanobiology in Cancer

To-date, most cancer research has focused on identifying genetic drivers of cancer and understanding the mechanism by which genes and specific signaling pathways in the cell drive tumor formation. Notably however, cancer, from tumor initiation through to metastasis and the formation of secondary tumors, involves both genetic changes within a cell and physical changes to tissue structure and the cancer cells [2]. As such, more recent work has now also focused on the mechanobiology of tumor progression. Mechanobiology is the study of how forces (e.g. pressure, tension and fluid flow) as well as mechanical properties (e.g. stiffness and elasticity) affect cellular function.

More recent advances in engineering and the physical sciences have uncovered critical roles of the mechanical and structural properties of both cells and tissues in guiding malignancy and metastasis. Indeed, it is becoming increasingly appreciated that tissue architecture and the mechanical properties of tissues and cells contribute to cancer progression. The ability of cells to exert force against their surroundings, as one example, enables the rearrangements of tissue fibers and the creation of paths through the tissue that facilitate metastatic cell movements[3, 4]. The ability to generate these forces is enhanced in tumor cells compared to their healthy counterparts[5], suggesting that metastatic cells are better at invading tissue because, in part, they are better at manipulating tissue by physically rearranging it to create paths in which they can move. Moreover, more metastatic cells have been shown to be more deformable than non-metastatic cells [6, 7]. Studies have suggested that this deformability helps metastatic cells

squeeze through tissue to escape the primary tumor and enter the circulatory system to move to secondary sites.

In addition to changes in the physical properties of the cells themselves, changes in the physical properties of the tissue itself have been shown to promote cancer progression. Solid tumor tissue is known to be stiffer than normal tissue, and research suggests that this stiffness can promote tumor cell growth and invasion. Moreover, decreasing tissue stiffness has been shown to delay tumor progression[8, 9]. These results indicate that tissue mechanics plays a critical role cancer, and that clinically, approaches to intervene with cancer mechanobiology have the potential to benefit cancer treatment.

Tissue-Engineered Platforms to Study Mechanobiology in Cancer

To investigate and manipulate the mechanobiology of cancer, tissue-engineered platforms have been critical. Since it is known that there are distinct differences between how human tumors form and grow in the body compared to how cancer cells grow in culture dishes or in animal models, tissue engineered platforms serve as bridges to better understand and manipulate the drivers of cancer. Using principles from biomaterials science, mechanics, and chemistry, engineers have been working to create platforms that recreate the architecture, chemistry and mechanical properties of the tumor microenvironment [2, 10]. These platforms will allow a greater understanding of the physical forces and features that drive tumor progression, and they have also in many cases been adapted for use as drug testing platforms.

Tissue engineered platforms can be created to mimic the dimensionality of tumors,

overcoming the limitation of conventional cell culture. They can also be created to mimic the stiffness and porosity of native tissue at various stages of tumor progression. More specifically, several bioengineering groups have developed tunable materials that mimic the changing mechanical properties of the tumor microenvironment. Materials that can be activated to stiffen or soften through various chemical techniques have been created and utilized to study how cells respond to the dynamic mechanical environment in tumor tissue[11, 12]. They can potentially be used to parse apart the effects of genetic changes from those induced by changes in the mechanical environment of the cell.

Translating Mechanobiology Into the Clinic

One of the biggest hurdles the field of cancer mechanobiology faces is the translation of findings into the clinic. For instance, since it is known that more metastatic cells exert higher forces and are more deformable, there may be clinical value to assaying patient samples to correlate forces and deformability with patient prognosis. It has been suggested that new mechanobiological assays can be incorporated into clinical protocols, and significant strides are being taken to develop assays that are user-friendly and translatable into clinical settings[13].

Clinically targeting mechanically-related molecules may also be feasible. There are numerous signaling pathways and associated proteins within cells that control cellular force profiles, cell contractility, and cell deformability. In fact, many of these pathways have been either directly or indirectly pharmacologically targeted in several other disease states including arthritis, diabetes, cardiovascular disease, and pulmonary diseases. Additionally, approaches to alter the mechanical properties of tissues have been developed for targeting tissue stiffening in wound healing and cardiovascular disease. As such, clinically treating changes in the mechanical

properties of cell and tissues is feasible and within reach.

Summary

The field of cancer mechanobiology has grown significantly over the past decade as the role of mechanical forces in cancer has been increasingly appreciated. It is now well-accepted that mechanical changes in both cells and tissues can contribute to malignancy and metastasis, however we have yet to fully understand the mechanisms by which mechanics promotes cancer. Engineers have the unique skills to build platforms to measure, probe and manipulate cell and tissue mechanics to better understand cancer mechanobiology and translate it into the clinic.

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