The Unexpected Control Behind Uncontrolled Growth

Cancer is scary. I've spent much of my time since high school thinking about cancer, investigating cancer, wondering about cancer. Now a sophomore at MIT studying biology and having done cancer research since high school, I've watched cancer cells multiply in dishes, seeded them in mouse organs, and dissected the various parts of each resulting tumor. Yet, it still knocks the breath out of me when I consider how cancer can affect people.

For the longest time, I thought of cancer as a thin film of cells that covered the bottom of cell culture plates that I used in the lab. I grew these cells by the billions. I characterized these cells by the time it took them to multiply enough to close a gap, the speed at which they travelled across a membrane, and the efficiency with which they multiplied and divided. The quantifiable speed by which they can take over a dish is nothing compared to the perceived speed by which they can ravage a person's body. Outside of a living host, they seem innocuous.

Yet, I know that these are the cells that ravage a person's body, growing infinitely and forming grotesque structures that crowd out and debilitate normally functioning cells. I know that these cells are responsible for the difficult chemotherapy and radiation therapy that patients endure. I know that cancer is the cause for mourning families and heartache in millions of people. These are the reasons why cancer is scary, why people fear their loved ones getting cancer.

Cancer is the second most common cause of death in the United States, accounting for 1 in 4 deaths, according to the American Cancer Society [1]. Furthermore, cancer has also become the primary cause of death in the United States for people under 85 years old, surpassing even heart disease, evidencing that deaths due to heart disease are declining faster than deaths due to cancer, according to the *Journal of the National Cancer Institute* [2]. In 2015,

it is estimated that 589,430 people will die of cancer in the US. Cancer also accounts for 1 in 7 deaths worldwide, an increase in prevalence from 1 in 8 deaths since 2013, only two years ago, with 60% of all recorded cancer cases occurring in less affluent countries, based on statistics from the American Cancer Society [3].

It's hard to understand the scope of cancer. It's familiar, it's widespread, and it's intellectually interesting, even. Yet, it's difficult to understand how cancer manifests itself in so many different forms to turn the lives of so many people upside down. One key to unlocking this puzzle is by solving the mechanisms of cancer metastasis which drive the severity of most cancers.

The Basics

Cancer cells arise from cells that have lost their mechanisms controlling how they divide and grow, usually becoming cancerous through acquiring several mutations in a process called transformation [4]. Typically, according to the National Cancer Institute, cancer progression can be characterized by a series of four stages, with stage 1 referring to a small tumor, or a growth of cancer cells, localized to a single place in the body, to stage 4 referring to an aggressive cancer that has spread throughout the body and colonized distant tissues and organs with tumors [5].

Typically, metastasis, in which cancer spreads from a single part in the body, will occur in stages 3 or 4 of disease. Metastases are highly lethal and notoriously difficult to treat. In fact, cancer itself can't be considered deadly; cancer metastases are [6]. As noted in multiple studies in *Nature Reviews,* more than 90% of cancer-associated deaths are due to tumors that have metastasized [7].

Cancer has long been studied from various perspectives including immunotherapy, using the patient's own immune system to target the cancer in their body, and tumorigenesis,

understanding how tumors are generated and targeting the beginning stages of growth, but researchers have pinpointed metastasis as the limiting step between patient death and patient survival. Given the lethality of metastatic cancer, many scientists are now focusing their efforts on preventing metastasis. In order to target metastasis, it is important to understand and characterize the mechanisms that contribute to the regulation of cancer metastasis. One method that has been heavily pursued and holds great potential is to target various biomarkers associated with metastasis. This method has in fact been my focus in research and may allow both identification of patients at risk of metastatic cancer and biomarker-targeted treatment, therefore stopping cancer before it has the chance to metastasize.

Main control mechanisms

It's easy to think of cancer as a monster. It seems like the perfect villain: growing uncontrollably, mutating to become stronger every minute, and taking over the human body from the inside, using the very being from which it originated as a host. Yet, to the cancer cells, we are the enemy. Our bodies are hostile environments, filled with scary molecules and immune cells from our immune systems that it must combat. We are relentless. Our bodies are constantly fighting against the cancer cells, and we constantly bombard them with drugs and other cancer treatments. In order to survive, they must go through a series of adaptations and acquire a set of special skills. Like any other living organism, their goal is just to survive; in order to survive, they must learn how to spread throughout the body and evade attack by other molecules and cells. Cancer may not be evil, but it is smart.

Typically, when cancer begins growing, it grows as an isolated tumor confined to a specific tissue. When it starts getting larger, because cancer cell growth happens relatively inefficiently with little structure, it becomes harder for cells on the inside of the mass to get the nutrients that they need [8]. To remedy this situation, cells on the outside will begin to recruit

blood vessels to the tumor in a process called angiogenesis. The increased blood flow from the new blood vessels helps deliver nutrients and oxygen to the inside of the tumor and allows the mass to grow even larger [9].

However, at some point, even recruiting new blood vessels is not enough to maintain the level of nutrients and oxygen needed to support the tumor mass, and cells start breaking away from the main tumor [8]. This begins the process of metastasis, and the main motivation to escape the main tumor is so that cancer cells can continue growing and proliferating with maximum speed. After it escapes from the main tumor mass, it becomes very difficult for the cancer cell to survive [10]. The most efficient method of travel to seed and colonize a secondary site is through a process called the metastatic cascade [11].

In order to begin the metastatic cascade, the cell must become motile and migratory, a stark difference compared to when it is safely nestled in a tumor adhered to numerous other tumor cells [12]. In order to disseminate and colonize a new place in the body, the cancer cell faces a new challenge; it must figure out how to move large distances efficiently. Although cancer cells by this point have become relatively motile, they still cannot travel large distances well. Thus, they must individually attack and enter the bloodstream from a vessel near the site of their primary tumor, using the system of blood vessels throughout the body like a highway system [11]. However, with greater speed comes greater risks and dangers. The bloodstream, flooded with various components of the immune system, is one of the most dangerous places for a cancer cell to be. Entering by itself is particularly dangerous, yet a cancer cell has no other choice. It cannot enter in a clump of cells because it is harder for a clump of cells to evade immune detection in the bloodstream, and it faces a greater risk of getting stuck inside the bloodstream [10].

A metastatic cancer cell's mission is not finished just by entering the bloodstream. In order to successfully spread, it must exit the bloodstream and colonize a new tissue [11]. After evading immune detection and reaching a suitable secondary site, the cells must stop travel and exit the bloodstream, setting up camp in a new microenvironment. This is the end of the journey for the cell, but by no means is its work over [13].

In order for this single cell to develop into a successful metastasis, it must be able to invade its new environment and proliferate quickly, creating micrometastases, or conglomerations of several cancer cells which can grow into secondary tumors [11]. This is especially important, because it is easier for several cells to recruit the necessary nutrients and to rely on each other for survival for long periods than it is for a single cell [10]. At this point, the cell must suppress its migratory phenotype and reactivate its adhesive phenotype, where phenotype refers to an organism's observable characteristics as governed by its genetic makeup. These new tumors can now recruit new blood vessels through angiogenesis, continuing the metastatic cascade.

Despite being the most efficient method of metastasis, this process is not easy. Cancer cells that reach this stage of development have undergone many mutations, at least two and usually many more, which give them the properties that allow them to undergo metastasis [13]. What makes metastasis even more complicated is that different portions of the metastatic cascade requires the cell to function differently. To deal with these demands, the cancer cell must develop multiple methods to regulate its own activity and to correctly time these various actions to regulate its interaction with its environment.

Fighting fire with fire

Although cancer maybe not be inherently evil, it is most definitely not healthy for its host. Typically, cancerous tumors are most effectively treated by surgical excision of the

cancerous tissue, as long as it has not spread to other places in the body. However, when it has spread, more drastic, blanket treatments must be utilized. Doctors must resort to such treatments with metastatic cancer because they have the ability to reach various parts of the body all at once. However, such strong treatments often have strong side effects, such as hair loss and nausea with chemotherapy, and damaged skin with radiation. Typically, these treatments, though necessary, aren't desired or well-tolerated because they end up harming healthy cells as well as cancerous cells.

The harm caused to healthy cells is responsible for the physical side effects of typical cancer treatments. For example, chemotherapy is essentially introduction of a cocktail of lethal chemicals into the body. Chemotherapy works because cancer cells are typically less well formed than normal cells and are thus slightly more sensitive to the presence of such harsh drugs; however, because normal cells are not immune, many times normal cells in addition to cancerous cells will die as a result of chemotherapy. The loss of such normal cells is characterized by dreadful side effects such as hair loss, because the hair follicles are unable to create more cells, or nausea, because the digestive cells have been damaged. Similarly, radiation is done through aiming high energy beams at cancerous cells, in order to kill them. For this to happen, healthy cells are also exposed to such radiation; while cancer cells are more likely to succumb to the high energy beams, they can also harm normal cells, causing injury to the skin surface that is touched by radiation.

As a result of such invasive treatment, much of the time, patients undergoing treatment for metastatic cancer will suffer from a compromised immune system. Such compromise is extremely dangerous, as the patient's body must actively work to fight off both the cancer and any incoming pathogens from the outside world, including anything from the common cold to antibiotic resistant staph bacteria (MRSA). In such a weakened state, the patient will

commonly succumb from the combined forces of the metastatic disease and other pathogens that it encounters.

Time to beat cancer at its own game

Given the many side effects and dangers of the current treatments, researchers are trying to discover other treatments for metastatic cancer. Because cancer is typically not lethal until it reaches the metastatic stages, a seemingly simple approach would be to catch cancers before they become metastatic. Yet, this has proven to be difficult because cancers behave considerably differently depending on their type and origin, and the tests that we currently use to help recognize the presence of cancers, for example imaging methods such as CT and PET scans, are not sensitive to small tumors, especially if they arise in organs sandwiched between other organs [4].

Recently, scientists have been finding and targeting biomarkers, or specific genes and protein products, that may be involved in the progression of metastatic disease. Typically, these biomarkers are useful because they can be found and quantified in relatively noninvasive ways, by looking and assaying for them in the blood or urine of patients. These biomarkers are especially targetable because not only do they signal the presence of a tumor, but they also function in the process by which primary tumor cells become metastatic. Therefore, they can be used to both find and treat disease [8].

One such molecule, as described in the *European Journal of Cell Biology,* is the activated leukocyte cell adhesion molecule (ALCAM), basically a protein product of white blood cells that functions in cell adhesion [14]. Described in a paper featured in *Cancer Genomics and Proteomics,* normal ALCAM function helps cells stick to one another because ALCAM molecules can adhere to other ALCAM molecules on adjacent cells, creating a network of ALCAM-ALCAM adhesions [15].

One previously mentioned aspect of metastatic tumor cells is that they have unnaturally robust control of adhesion, which allows them to successfully progress through the stages of the metastatic cascade. During some steps they have to be able to stick to other cells, such as when they establish their secondary sites, but in other steps, such stickiness would be detrimental, such as when they are trying to travel through the blood stream. If they are unable to have robust regulation of movement, then they will get stuck in a step. One way they regulate such movement is by regulating their adhesion molecules.

ALCAM is an example of an adhesion molecule regulated in order to facilitate robust cancer cell motility, as described in *Cancer Research.* Although ALCAM normally has the ability to adhere to itself on other molecules, the portion that does the adhering can be cleaved, or cut off by another protein. This causes the cell to be able to begin the processes of metastasis. This form of the protein is called shed ALCAM, and this form of ALCAM can be used as a biomarker for metastatic disease [16].

The idea of ALCAM as a biomarker has been clinically supported by studies in the *Journal of the National Cancer Institute*, which has evidenced an increased, or upregulated, level of shed ALCAM in patients with poor prognosis, or patients who have died or are likely to die from late stage metastatic cancer. ALCAM may be a remarkably good biomarker especially because up regulated levels of ALCAM have been seen in all cancers that form solid tumors [17].

With an increased understanding of the forces that drive cancer metastasis, and an increased understanding of the biological molecules involved in cancer metastasis, it is our hope that in the future we will be able to leave behind the invasive and painful methods of treatment that are currently utilized to treat metastatic disease. Ideally, with increased

understanding of the beginning stages of metastasis, it will be possible to identify pre-metastatic lesions and prevent such metastasis from a molecular standpoint.

It is this hope which drives me to return to lab day after day, looking into the microscope or pipetting for hours. Cancer structure and function intrigue me, the nature of research and discovery through collaboration excite me, but it is the mystery, devastation, and scope of human disease that motivate me day after day. I strive to contribute to the force that is learning to control metastatic cancer. And there is no better time to do it than now.

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