They’re moving like an army does as it enters a war zone, marching through the bloodstream, recruiting cells to multiply, bombarding the human body’s organs, and seizing the land of life. While the war on cancer continues, scientists have been devising a plan to target metastasis, the spreading of cancer cells from the original tumor to other parts of the body, that could halt the marching cell troops in their tracks and destroy the enemy.

In metastatic cancer, otherwise known as stage four cancer, cancer cells spread to other parts of the body by breaking away from the original tumor and entering the bloodstream or lymph system. The cells then attach to the wall of a blood or lymph vessel, using it as a passage-way to a new organ, and then grow in their new home while dodging security: the immune system. These traveling cancer cells can cause new blood vessels to grow, providing a blood supply that fuels the growth of the tumor. As a result, stage four cancer survival rates are very low. For instance, in 2016, the American Cancer Society estimated that the five-year survival rate for stage IA melanoma (skin cancer) was 95% while stage II A was 81%, and stage III A was 78%. The predicted survival rate for stage IV melanoma, on the other hand, was given a mere 15-20%, an immense drop of expectation and hope for anyone diagnosed with metastatic skin cancer. Therefore, current research has been aimed at halting the migration of cancer cells, hoping to improve these survival rates for stage IV patients.

To inhibit cell movement, researchers must target the specific components of a cell that work in tandem to produce movement. Two of the main components include integrins and the cytoskeleton. Within each eukaryotic cell is the cytoskeleton, a structure composed of filamentous proteins that coordinates cell movement, growth, and division, and as well as the movement of organelles within the cell. Among the three major types of filamentous proteins are two which guide cell motility: microtubules and actin filaments (see figure 1). Microtubules serve as each of the cells very own taxis, transporting organelles throughout the cell. They also combine to form cilia and flagella to help the cell move. Actin filaments aid cell movement by sliding along myosin filaments, which then causes cells to contract and provides the force needed to initiate cell migration. Cell motility is implicated in a variety of crucial physiological processes including reproduction, the elimination of waste, and cardiac muscle function. However, when metastasis enters the cell highway, bloodstream traffic becomes unregulated and drastic action must be done to police the components of the cytoskeleton to inhibit cell movement. Integrins, receptor proteins that modulate the cytoskeleton and regulate cell mobility, have become a target for drug development in combating metastasis because previous studies have shown these proteins to be genetically under or over-expressed in cancer cells (9). Furthermore, inducing expression of certain integrins such as the αvβ3 integrin increases the potential for metastasis (4-5).

Building upon previous research, Ali et al. (2017) continued studying integrin regulation, but took the research a step further by fitting four previous research puzzle pieces together. One: Arg–Gly–Asp (RGD) peptides (smaller protein pieces) bind to a variety of surface integrins (8, 16-17). Two: gold nanoparticles (AuNRs) have been shown to inhibit the assembly of the actin cytoskeleton, thereby decreasing cell migration (20). Three: By exposing Near Infrared Light (NIR) to AuNRs, heat can be generated (3.7, 10). Four: Heat stress affects the cytoskeleton, resulting in its rearrangement (2, 6, 12). Thus, by linking the RGD peptides that bind to the integrins with AuNRs and exposing the AuNRs with light, Ali et al. (2017) could test the inhibitory effect of heat on cell motility and uncover a molecular mechanism that allows cells to move. Their results hold promise for keeping this cell traffic under control.

To explore the molecular mechanism involving integrins and the regulation of the cytoskeleton, Ali et al. (2017) targeted the AuNRs to the integrins of human carcinoma cells (cancer cells of the epithelial tissue) by binding them to the surface of RGD peptides and exposing them to NIR light to generate heat when the peptides would bind to the integrins (AuNRs@RGD+ NIR). Moreover, three additional treatment groups were studied: the control/healthy cells (Ctrl), non-integrin targeted AuNRs (AuNRs) and AuNRs targeted to the integrins but unexposed to NIR light (AuNRs@RGD). Ali et. al. (2017) investigated both qualitative and quantitative cell characteristics and discovered that cell migration became inhibited in all experimental conditions, leading them to determine a possible map of signals that are involved in controlling cell motility.

On the qualitative side, Ali et. al. (2017) introduced a wound into the cells of each of the four condition types and took cell images at the start of the experiment and twelve hours after, analyzing changes in cell morphology using a microscope. Upon examining the cells after twelve hours, Ali et. al. (2017) reported that the cells in the control group completely healed whereas the cells in the other three conditions did not as cell movement is essential for the healing process. The AuNRs cells did not completely heal and AuNRs@RGD cells showed even less healing. The AuNRs@RGD+NIR cells healed the least out of all four groups, demonstrating the increased inhibitory effect of targeting integrins and exposing the cytoskeleton to heat. The lab team was slowly developing the weapon of inhibition.

To construct a map of a series of molecular signals that control cell movement, Ali et al. (2017) quantified protein expression changes in migration-related pathways. About 1,800 proteins were quantified in the four treatment groups using a heatmap (a certain color represents over-expression or under-expression) and Western blot analysis (within an array of protein bands the thickness of the band reveals how much protein is present). As expected, AuNRs@RGD+NIR cells resulted in the greatest changes to the migration related pathways, followed by the AuNRs@RGD and then the AuNRs. Now the investigative scientists were ready to connect the dots. Cell migration is regulated by AuNRs in four main ways. Many proteins involved in signaling cell contraction by actin-myosin were under-expressed. Secondly, actin-binding proteins were downregulated; weakening the connection between the cytoskeleton and integrins. Third, microtubule-associated proteins were also down-regulated, disrupting the assembly of the microtubules, and possibly limiting cell movement. Lastly, different kinases, enzymes involved in the signaling pathways, that were altered are associated with integrin regulation and cell migration. For example, the protein EGFR (epidermal growth factor receptor) decreased shown by western blot analysis (see figure 2). At
last, a map was created to represent possible protein-signaling mechanisms involved in cell motility (see figure 3).

By manipulating the cytoskeleton via integrin targeting and applying heat to the cytoskeleton to understand the various proteins impacted, Ali et al. (2017)’s recent work offers a significant contribution to our understanding of the signaling of migration pathways of cells. Proteins involved in the cell migration pathways were down or up-regulated which caused a cascade of signaling interruptions, ultimately inhibiting cell movement. Further, cells in which the cytoskeletons were exposed to heat exhibited a greater magnitude of this effect. Given these results, in the future cancer cell packs could be stopped before they even break away from the tumor, and survival rates could improve dramatically. One thing is for certain: nanoparticles seem to be a promising technology for future research, paving the way for inhibitory treatment to conquer cancer.

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References


