Science Education Collection

An Introduction to Cell Motility and Migration

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Abstract

Cell motility and migration play important roles in both normal biology and in disease. On one hand, migration allows cells to generate complex tissues and organs during development, but on the other hand, the same mechanisms are used by tumor cells to move and spread in a process known as cancer metastasis. One of the primary cellular machineries that make cell movement possible is an intracellular network of myosin and actin molecules, together known as “actomyosin”, which creates a contractile force to pull a cell in different directions.

In this video, JoVE presents a historical overview of the field of cell migration, noting how early work on muscle contraction led to the discovery of the actomyosin apparatus. We then explore some of the questions researchers are still asking about cell motility, and review techniques used to study different aspects of this phenomenon. Finally, we look at how researchers are currently studying cell migration, for example, to better understand metastasis.

Transcript

Cell motility is required for many physiological and pathological processes, including cell migration during embryonic development, movement of white blood cells in response to infection, and cancer cells undergoing metastasis. Two cellular proteins, actin and myosin, form the principal building blocks of the motility apparatus.

In this introductory video, we’ll review some of the landmark discoveries in the field of cell motility and migration. Then, we’ll highlight a few unanswered questions regarding cell motility, followed by a discussion of classical and advanced tools used to study motility. Finally, we’ll wrap up with some example experiments.

Let’s start by looking at the important discoveries associated with this field.

In the 17th century, Anton van Leeuwenhoek, with the help of a microscope, became the first person to observe the movement of spermatozoa and bacteria. A couple of centuries later, Theodor Wilhelm Engelmann and Wilhelm Pfeffer discovered stimulus-driven bacterial motion, including: phototaxis, which is movement influenced by light; chemotaxis—movement towards various chemical substances; and aerotaxis—movement in response to oxygen. Around the same time, Ilya Metchnikoff performed a fascinating experiment in which he pricked the transparent starfish larva with a rose thorn, and observed cells moving from other parts of the body to the wound. This led to the notion of leukocytes migrating to a site of injury, pioneering the field of immunology.

An understanding of the mechanism of cell movement began a few years earlier, when studying a seemingly unrelated phenomenon—muscle contraction. In 1859, Wilhelm Kühne isolated a muscle protein that he thought was responsible for its stiffness, and called it myosin.

In 1942, Brunó Ferenc Straub discovered that the “myosin” preparations actually contained a secondary protein, actin. We now know that actin and myosin interact to form the actomyosin complex, which produces contraction. In 1974, Margaret Clarke, while working under James Spudich, characterized actomyosin-like structures in the slime mold *Dictyostelium*, and suggested its involvement in non-muscle cell movement.

In 1983, Spudich, along with Michael Sheetz, developed an *in vitro* actomyosin model, which paved the way to our present-day understanding of their mechanism. We now know that ATP, a “high-energy” molecule in cells, binds to myosin and powers the myosin molecule to “crawl” along a parallel actin molecule, thereby generating a contractile force that in non-muscle cells can pull the cell forward during migration.

After the brief historical outline, let’s discuss a few questions about cell motility that scientists are asking today.

Researchers are interested in learning how environmental cues direct cell movement. Cells move in response to a variety of signals, including those that drive embryonic development, or alert immune cells to sites of infection. These signals are usually chemical compounds released by some cells to induce migration of a specific type of cells towards them. Therefore, studying the mechanism of this chemotaxis induction can help scientists better understand the disorders in which cell migration is disrupted.

Another important area of investigation concerns the molecular machinery that cells use to move. In addition to the actomyosin apparatus that allows cells with flexible shapes to extend protrusions and “crawl” along surfaces, researchers also seek to understand how cell motility can be driven by other cytoskeletal elements, such as the microtubules that form the “shaft” of sperm tails, as well as the complex molecular machines that form bacterial flagella.

Finally, some scientists explore how cells interact with each other and migrate together in groups, which occur in early embryogenesis, as well as the wound healing process.

Additionally, because cells in the body actually exist within a mesh of molecules known as the extracellular matrix, abbreviated as ECM, investigating how cells interact with and invade into the ECM can help in understanding phenomena such as cancer metastasis.

Now that we have an idea of the questions being asked in the field, let’s learn about some prominent techniques being employed.

The scratch assay is used to model how epithelial cells repopulate an open area—a process similar to wound healing. In this procedure, a wound is created by running a pipette tip through the cell culture dish. As cells grow back into this gap over time, their movement trajectories could be tracked using tracking software to assess movement speed and displacement.

The transwell migration assay is another classical method used to study chemoattraction, which is the process of chemically attracting cells. In this assay, chemoattractant solution is added to wells, then the transwell chambers are placed inside these wells, and finally, a migratory cell type is added on the upper side of the membrane. The number of cells migrating towards the chemoattractant can be counted using a microscope and hemocytometer.

Advances in engineering techniques have allowed the construction of microfluidics devices, composed of microfabricated channels etched on a suitable surface. For migration experiments, the channel usually has two ports: one for the addition of a cell suspension, and another for the addition of a chemical stimulus. The effect of the stimulus on cells' migratory behavior can then be studied under a microscope.

To study the invasion of cells into the ECM, researchers can perform 3D invasion assays. In this method, scientists culture cells in three-dimensional matrices made of components such as collagen. Then, with the help of sophisticated software they can track invasion in three dimensions. This method is particularly useful for studying tumor development.

Finally, time-lapse fluorescence microscopy can be used to track live cells *in vivo*. Genes encoding fluorescent proteins can be introduced into an animal model. The migratory path of the cells now expressing fluorescent proteins can be traced using sophisticated imaging methods, such as two-photon microscopy.

Now, let's examine some current applications of these cell motility and migration assays.

As discussed, cell migration plays a critical role in tumor metastasis. Here, scientists cultured tumor cells embedded in a matrix together with brain slices in a transwell chamber. Following incubation, the samples were stained and analyzed using immunofluorescence. Results demonstrated invasion by tumor cells into the brain slices.

Following infection, cells release chemokines, which are chemoattractant proteins that induce migration of neutrophils. Neutrophils are phagocytic cells, which form an integral part of the innate immune system. Here, researchers evaluated this phenomenon using a transwell migration assay. They plated bacteria-infected epithelial cells onto the underside of the membrane, while neutrophils were cultured on the upper side. Results showed significant neutrophil migration in the presence of infected cells.

Finally, microfluidic chamber assays can be used to examine bacterial chemotaxis. Here, scientists evaluated attractant and repellant properties of two substances—L-aspartate and nickel sulfate—using a specialized microfluidic chamber that could test several concentrations in one experiment. The data obtained demonstrated that with an increase in attractant and repellent concentration, bacterial migration towards and away from the test molecules also increased, respectively.

You've just watched JoVE's introduction to cell motility and migration. In this presentation, we reviewed the major milestones in the study of cell motility and migration. Next, we discussed some current questions being asked, and tools being used in labs today. Lastly, some example experiments highlighted applications of these techniques. As always, thanks for watching!