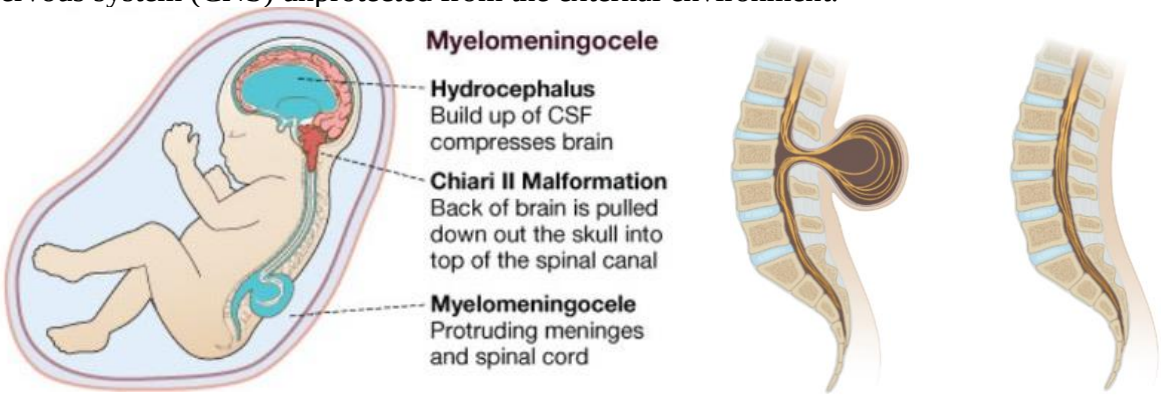
Targeted Delivery for Treating Spina Bifida

By Tyler Sickler

Imagine you are on a boat and it suddenly starts to fill with water. Patching the hole responsible is doable, but you are also worried about the valuable items on board that could become damaged by rising water inside your boat. Take a second to think about what those items could be—your phone, food, maybe even a navigation system to help you get back to shore. Whatever it is, life would sure be more difficult without it. Now let's consider a condition called spina bifida.

In human development, a structure called the neural tube develops into the spinal cord. The spinal cord is a very important structure that sends messages between our brain and different parts of our body that allows us to walk, run, jump, and more. In fact, think of anything your body does—odds are good that the spinal cord has a role in that activity.

A condition called spina bifida can interrupt the function of the spinal cord. Spina bifida develops during gestation when a fetus' growing spinal column does not completely form a tube. The cells of the developing spinal cord first form a flat sheet-like structure before the cells on the periphery rise up to form ridges that eventually merge in the midline to form a tube. Spina bifida is considered a "closure defect" because the merging at the midline does not happen all along the forming tube (Figure 1). The opening that is left provides an entry point for the surrounding fluids to damage the delicate tissues of the spinal cord. Similar to a hole in the bottom of a boat, when there is a breach in the neural tube of a growing baby, this event leaves cells of the central nervous system (CNS) unprotected from the external environment.



The resulting damage includes varying levels of paralysis, inability to control their bladder, and requires these individuals to have lifelong shunts to drain excess cerebral spinal fluid around the brain.

Fortunately, there has been a recent breakthrough in treating spina bifida. Currently, the standard of care for spina bifida patients is pre-natal in utero (within the uterus) surgical repair of the malformed neural tube. Performing this type of surgery before the baby is born decreases the amount of progressive damage during pregnancy and gives the baby a better chance of being able to walk and have less severe secondary symptoms. Unfortunately, the result of this

procedure cannot restore any neurological function that had already been lost by the time of surgery [2].

This begs the question: What can we do to rescue lost neurological function that might otherwise leave the patient paralyzed?

To improve patient outcomes, stem cell therapy has been used alongside in utero surgery in research to protect the at-risk neurons of the spinal cord from the secondary effects of spina bifida. Mesenchymal stem cells (MSCs) are a type of stem cell that can give rise to numerous tissues types and can also release factors that can repair damaged tissues. Amongst these secreted factors extracellular vesicles (EVs) are perhaps the most valuable. EVs play an important role in how cells talk to one another [3,4]. Acting as tiny mail trucks, they deliver different types of RNA and proteins to nearby cells.

In the context of spina bifida, the RNA inside these EVs act as a survival guide for the receiving spinal cord cells. Meanwhile, the proteins that reside in the EVs can readily promote protection of neurons and supply them with other necessities. However, one important question remaining in the field is—how can we get the most out of EVs?

One of the challenges in answering this questions is finding an efficient way of delivering EVs to the spinal cord. In a recent study, scientists tracked stem cell derived-EVs following injection. They discovered that a majority of EVs direct their delivery of supplies to the spleen and liver, while very few ended up in the central nervous system [5]. One way to better help these EVs find their way to neurons is by giving them the directions they need.

To provide these directions, specific proteins can be added to the surface of EVs to help guide them to damaged areas by allowing them to access specific cell types. For example, the rabies virus uses a special protein on its surface to trick neurons into letting them in. One idea is to implement this special protein in directing the EVs to the neurons, but for the delivery of therapeutic factors—and not harm! This is a safe and efficient way to bring EVs to the site of injury and has even been previously used to help treat mice with Alzheimer's disease.

This brings us to work I will be doing in the laboratory of Dr. Wang at the University of California, Davis—Department of Surgery.

I will be using stem cell-derived EVs and sticking this special rabies virus protein on their surface in the hopes of causing an enhanced neuroprotective effect in a rat model of spina bifida. The success of these results could lead to even bigger steps towards treating spina bifida patients and those suffering from other neurological diseases.

References

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