

Stem Cells and Tissue Healing in Horses

Healing - "fill the defective area with a tissue that is as close to original as possible" to allow the horse a full return to function. Bone, ligament, and tendon were areas in which equine stem cells have been used most frequently. Bone cells are the best healers, generally forming the most complete and strongest repair; ligament and tendon cells are more likely to form weaker and more "disorganized" tissue that is more likely to fail after healing.



The first phase of healing is the "inflammatory stage". During this stage (generally the first five to seven days after injury) the injured tissue releases molecules called cytokines that initiate the healing process and clean up the area around the defect by removing dead tissue. Specific cells also invade the area and help remove debris, preparing the environment for the arrival of "replacement" cells. Blood flow increases to the area and the blood clots, forming the first type of "scaffold" in the damaged area (the scaffold effectively helps the new tissue "know" where to grow).



Nature Reviews | Immunology

Traditionally (without the aid of stem cells) during this phase, horses are treated with non-steroidal anti-inflammatory drugs (NSAIDs) and local anti-inflammatory therapy such as application of ice or poultices.

The second phase of injury healing is the "fibroplastic stage," which lasts for several weeks or months (depending on the severity of the injury). During the fibroplastic stage the cells responsible for healing the defect are "recruited" and the healing process begins. This is when cells appropriate for healing tendon, bone, and ligament begin to regenerate tissue. Traditionally, veterinarians recommend that horses begin range of motion and light weight-bearing exercise during this phase and continued treatment with NSAIDs .

The final phase of healing (which can last for several years) is the "remodeling phase." During this stage the cells complete regeneration, organize to form a proper "matrix," and that especially in bone healing, they remove any excess callous tissue that has formed. Horses return to work during this stage. Gradually, the horse's workload is built up in hopes of returning to the pre-injury level of work.



Traditional Treatment Options and the Problems

1. Veterinarians regularly recommend rest for many horses with tissue injuries, and while this proves successful in many cases, but it can be quite difficult for certain horses to actually stay quiet or "controlled" long enough for the defect to heal. Attempting to expedite healing with regenerative medicine approaches would aid in returning horses to function sooner and without the distress of prolonged layup times.
2. Anti-inflammatory and intra-articular (joint injections) medications are popular treatment options; however, these are essentially treating the symptoms of injuries rather than the cause. Intra-articular medications are good options for treating degenerative joint disease and arthritis (which to this point can be contained but can't be cured).
3. Arthrodesis (joint fusion) is one popular choice for dealing with some specific joint injuries; however, this treatment option doesn't restore the tissue to its pre-injury form--it simply keeps the joint from moving and, thus, causing pain. Additionally, there tend to be hospital costs involved, which could be prohibitive for some owners. Surgery is always an option and in some cases required. However, the high costs associated with surgical procedures are prohibitive for some owners, and there's always a risk for complications (from anesthesia, for example).

There are a few potential problems that arise with the traditional methods of tissue healing, although there's little to nothing that can be done about these natural challenges:

- "Tendons and ligaments often heal with a disorganized scar tissue formation," meaning the structure is weakened and likely won't have as wide a range of motion, predisposing it to reinjury;



- Bones take a long time to heal properly; and
- When injured, joints can be affected with progressive cartilage damage, which traditionally has been difficult to manage.

What are Stem Cells?

Stem cells are, essentially, immature cells that can transform into whatever kind of cell they're prompted to become (more on that in a minute). Researchers have been working with a few different stem cell sources:

Embryonic stem cells are derived from fertilized embryos, and there's been hefty political and ethical debate on using these cells in human medicine. Using equine embryonic stem cells in horses isn't commonplace yet.

Fetal- and maternal-derived stem cells come from the umbilical cord blood and tissue and the placenta. Although collection was originally thought to pose a risk to mare and foal, studies have shown that collection is safe and has no effect on the mare or foal. Recent evidence also demonstrated that these "fetally" derived stem cells are effective sources for regenerative approaches.

Adult somatic stem cells, commonly known as mesenchymal stem cells (MSCs), are naturally present in a variety of tissues in the horse's body at all times. They're designed to replenish dying cells and regenerate damaged tissue.

The most commonly used stem cells in veterinary medicine are those from MSCs which can be collected from either adipose tissue (fat, which is harvested from the horse's hindquarters) or bone marrow (which is harvested from the horse's sternum or pelvis).



Veterinarians look for three specific criteria when determining if the cells collected are in fact MSCs:

- Firstly, MSCs will adhere to plastic culture plates during proliferation;
- Secondly, through a series of tests, the MSCs will demonstrate that they can form fat, bone, and cartilage tissues; and
- Finally, the cells must have genetic markers and proteins specific to MSCs.

Prior to administering stem cells, veterinarians will decide whether to use autologous or allogeneic stem cells. Simply put, the former are stem cells from the horse's own body that are reinjected after proliferation. The latter are stem cells harvested from a different horse's body. There are upsides and downsides to using each kind of stem cells:

Autologous cells are often thought of as safer to use than allogeneic, as they are native to the horse's body rather than from another horse. There are some concerns about the immune response horses might produce if injected with allogeneic stem cells; recent evidence, however, suggests that allogeneic cells do not cause adverse reactions when introduced in equine joints or injected in the skin.

Allogeneic cells are available for use more rapidly, as they must proliferate only for a few days rather than weeks after harvest.

Research indicates that some horses produce more and "better" stem cells than others (meaning the cells' characteristics are more predictable and consistent), so using allogeneic cells from a donor horse can mean higher-quality cells; and

Technically, allogeneic cells might be considered drugs because they're not derived from the horse's own body. Therefore, they might be subject to regulation, including careful product screening and the use of laboratory procedures that are sanctioned by the same governing bodies that regulate medications.

What Can They Do for My Horse?



There are several circumstances in which veterinarians suggest stem cell therapy for clients; however, the most common use of stem cell therapy is in tissue regeneration and repair during the fibroplastic phase of tissue healing. This means it is most likely that cell therapies are most efficacious a few weeks after a horse sustains an injury. It's pretty much agreed upon by most that the stem cell treatment should be most beneficial (in this phase of healing).

Researchers are also investigating use of stem cells to control inflammation caused by injury, so the use of stem cells in the acute phase of injury isn't out of the question.

Once enough stem cells have proliferated in culture dishes, veterinarians administer the cells in two ways: directly into a horse's lesion or through an intravenous catheter in a nearby area. Once inside the body, the stem cells are drawn to the affected area and then "recruit" cells in the surrounding areas of the body to aid in tissue regeneration and repair. Stem cells seem to allow injured tissues to heal in a more organized manner, increasing the healed area's strength and stability and decreasing the likelihood of reinjury.

What's Next?



There remains a lack of scientific research into stem cell therapy because in many cases in the recent past, stem cells were used as a "last-ditch" effort to heal a horse from injury. There are many institutions in which veterinarians are pursuing important research to answer these and other questions regarding the appropriate timing of treatment, the fate of cells once introduced in the tissue, and the use of scaffold or "matrices" on which to grow cells prior to implantation. Horse owners should seek information from reputable sources prior to making decisions regarding the use of regenerative approaches in their horses, keeping in mind that these therapies are offering promising results and (could) positively affect the way we treat equine injuries.