Paramedic Activity of MSCs Utilized in Tunable Hydrogel for Chronic Wound Treatment

By Nora Rimpo

Type II diabetes is a chronic disease that is sweeping our nation like a pandemic. The incidence of diabetes has soared from a meager 1% in 1960 up to 7% today, currently affecting 29 million individuals in the U.S.[1] An estimated $245 billion dollars are spent annually on diabetes related care.

Patients with diabetes are at an increased risk for developing wounds that do not heal. Current treatment options include gauze dressings or skin substitutes, which are biological or synthetic products that mimic properties of skin, to aid in wound healing.[2] Patients that do not respond to treatment require amputation to prevent death from life-threatening infections. Approximately 71,000 diabetic patients will require amputation each year.[3] Therapeutic advancements are urgently needed to provide patients with a better quality of life and to decrease the costly burden afflicted on our healthcare system.

Wound healing occurs like an orchestrated symphony, but the process can quickly go awry in a diabetic patient requiring therapeutic intervention.[5] The research lab of Dr. Maverakis at the Institute for Regenerative Cures, UC Davis, is developing a treatment option using mesenchymal stem cells (MSCs). This cellular therapy is based on cutting edge research and resembles a fancy cell-based band-aid.

So, what are MSCs and what do they have to do with wound healing? MSCs are a type of stem cell referred to as "multipotent." Multipotent means the MSCs have "multiple potentials" when they begin to develop into adult cell types. In the case of MSCs, their multipotency refers to their ability to develop into different connective tissue cells types (e.g., bone, muscle, fat, dermal cells), but nothing else. Studies have shown that MSCs also affect immune system activity; for example, they can promote healing through accelerated closure of wounds and also improve blood vessel formation.[6] In fact, MSCs are sometimes referred to as the "paramedics of the body" because of their ability to help repair damaged tissues.

To create a cell-based band-aid that can be placed over a wound to promote healing, a substance called a hydrogel is used. The hydrogel is made out of a compound called polyethylene glycol (PEG) and acts as a delivery platform for MSCs to the wound while also maintaining an optimal environment for MSC survival. The therapeutic benefits of MSCs would be useless if the cells could not be localized or survive long enough for their benefits to be realized. This is where our research comes into play.

You feel most relaxed when you are at home, right? MSCs act in similar ways. Their home is the human body and the cells can sense when their local environment changes. The hydrogel we plan

to construct will create a mock home for the cells that mimic the body's environment and allows for the cells to survive and thrive at the site of the wound.

In addition, the cells must be kept at the site of the wound and not allowed to wander off. Just as a person uses a leash to keep a pet nearby, we have developed a mechanism that maintains the MSCs at the wound area. This system works by using protein receptors called integrins that are found on the surface of MSCs. Integrins interact with the environment and signal to the cell. We found a new small molecule (a peptide) that MSC integrins specifically recognize. This peptide will tether the cells (via their integrins) to their surrounding environment and keep them from straying.

We have studied what this peptide-integrin interaction does to the cell and it appears to increase expression of genes that participate in wound healing. This finding is key for improvement of chronic wound therapies. Embedding the peptide in the hydrogel will both retain the MSCs at the wound area and promote healing.

The next step in our research will use a mouse model of wound healing to further study the peptide-integrin interaction. With this model we will be able to learn even more about the biological effects of the PEG hydrogel and provide more evidence to support initiation of clinical trials. Looking ahead, this MSC based therapy has the potential to solve a serious problem currently facing our healthcare system and improve the quality of life of millions of suffering patients.

References

[1]Geiss LS, Wang J, Cheng YJ. Thompson TJ, Barker L; Li Y, Albright AL, Gregg EW. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. JAMA 2014; 312:1218-1226.

[2]Center for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. U.S. Department of Health and Human Services, CfDCaPCenters for Disease Control and Prevention; Atlanta, GA: 2008.

[3]Halim, A. S., Khoo, T. L., & Shah, J. M. Y. (2010). Biologic and synthetic skin substitutes: An overview. *Indian Journal of Plastic Surgery*, *43*(3), 23.

[4]Bauer E. Sumpio, "Contemporary Evaluation and Management of the Diabetic Foot," Scientifica, vol. 2012, Article ID 435487, 17 pages, 2012. doi:10.6064/2012/435487

[5]Patrick S. Murphy and Gregory R. D. Evans. Advances in Wound Healing: A Review of Current Wound Healing Products, Plastic Surgery International, vol. 2012, Article ID 190436, 8 pages, 2012. doi:10.1155/2012/190436

[6]Chen, S. *et al*. Mesenchymal stem cell-laden anti-inflammatory hydrogel enhances diabetic wound healing. *Sci. Rep*.**5**, 18104, 2015. doi: 10.1038/srep18104