Math used as a tool to heal toughest of wounds

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(PhysOrg.com) -- Scientists expect a new mathematical model of chronic wound healing could replace intuition with clear guidance on how to test treatment strategies in tackling a major public-health problem.

The Ohio State University researchers are the first to publish a mathematical model of an ischemic wound - a chronic wound that heals slowly or is in danger of never healing because it is fed by an inadequate blood supply. Ischemic wounds are a common complication of diabetes, high blood pressure, obesity and other conditions that can be characterized by poor vascular health.

An estimated 6.5 million people in the United States are affected by chronic wounds, and many are at risk of losing limbs or even dying as a result of the most severe of these wounds.

Modeling by mathematicians with expertise in biomedical processes has become increasingly important in the health sciences. The modeling reduces the need for guesswork and time-consuming animal testing traditionally required as researchers pursue prevention, diagnosis and treatment of complex diseases.

"Before you treat any problem successfully, you have to understand it," said Chandan Sen, professor and vice chair for research in Ohio State's Department of Surgery and a senior author of the study. "Now that we have this model, we can take the next step to find what factors in the

equations can be fine-tuned to the point where the net result is improvement in the ischemic wound outcome."

The modeling research appears this week in the online early edition of the Proceedings of the National Academy of Sciences.

The mathematical model, to date, simulates both non-ischemic wounds - those typical of wounds in healthy people with good circulation - and ischemic wounds. The current model produced results that generally match pre-clinical expectations: that a normal wound will close in about 13 days, and that 20 days after the development of an ischemic wound, only 25 percent of the wound will be healed.

The model also showed that normal wounds have higher concentrations of proteins and cells expected to be present during the healing process, while ischemic wounds lack oxygen and remain in a prolonged inflammatory phase that interferes with the subsequent cascade of events required to begin wound closure.

Sen, also executive director of the Comprehensive Wound Center at Ohio State, recently published a report about a biological pre-clinical model of an ischemic wound that his lab designed using the skin on a pig's back. The new mathematical model, a system of partial differential equations, borrowed some data from the animal model, but also includes numerous calculations assigning values to the various cells and chemicals involved in the wound-healing process.

"Wound geometry is complicated because it is three-dimensional," said Avner Friedman, a senior author of the paper and a Distinguished University Professor at Ohio State. "It would be infeasible to perform our computations within the framework of this geometry. However, we used some mathematical ideas to reduce the problem to a simpler geometry without giving up any of the important aspects of the process."

It is not just the wound that is three-dimensional, the researchers noted. The complexity of this process is compounded by the fact that the wound-healing model must take into account both the total space occupied by the wound and the time required for the healing process.

Wound healing under normal conditions occurs in four overlapping stages: haemostasis, when platelets make clots to stop bleeding and release chemicals that attract cells to the wound; transient inflammation, when a variety of white blood cells go to work to kill infectious agents and generate growth factors needed for repair; proliferation, when new blood vessels form and when cells produce a bed, called the extracellular matrix, on which the repair occurs; and remodeling, which can take years, as the repaired wound site gains strength.

Sen and colleagues have spent years studying the characteristics of wounds and the intricate details of the healing process. Oxygen is a known essential element to the healing process, and high-pressure oxygen chambers are used to treat some wounds. But for ischemic wounds, oxygen alone isn't enough.

Scientists know that reduced blood flow to a wound site means that oxygen, important nutrients and circulating cells are not finding their way to the wound to initiate healing. Researchers hope that manipulating mathematical models of these conditions could offer guidance on how to approach this problem without the time and trial-and-error required in biological studies on animals.

"We're not just considering what type of therapy should be used for these wounds. It is the specifics of when and how you apply it - those are the details that matter," Sen said. "Mathematical algorithms provide more pointed data that biologists can use to develop hypotheses."

Developing the biological model was an important start, Sen and

Friedman noted. To create an animal model of an ischemic wound, researchers had to strike a careful balance so they reduced blood flow to the wound site without killing all the surrounding tissue by cutting off too much blood. Sen said the 8-millimeter-wide cylindrical puncture wounds rest on what the researchers consider an "island" of skin receiving too little blood to effectively deliver healing cells and chemicals to the wound. Details about the animal model are published in the May issue of the journal Physiological Genomics, a publication of the American Physiological Society.

In developing the mathematical model, Friedman worked with first author Chuan Xue, a postdoctoral researcher in Ohio State's Mathematical Biosciences Institute, to assign values to variables in the first two stages of wound healing. These included oxygen concentration, concentration of growth factors, density of white blood cells that fight pathogens, density of fibroblasts that perform part of the repair, and density of tips and sprouts of tiny new blood vessels.

The two also modeled the extracellular matrix - the bed on which cells work to close the wound - in a way that allows for the matrix to change the way it functions over time. This part of the model also allowed for simulation of the exertion of pressure - a characteristic of certain types of ulcers that people with diabetes are prone to develop.

Xue noted that the equations were borrowed from the mathematical theory of homogenization by manipulating a single parameter - called parameter alpha - to draw the distinction between ischemic and nonischemic wounds in the model. This is one example, Friedman noted, of simplifying the model without leaving out important biological details.

Source: The Ohio State University (news : web)