Immortal Human Skin Cells - A Miraculous Answer for Burn Victims?

Could skin cells that do not die at the University of Wisconsin, Madison, provide a better and unlimited skin supply for burn victims? Healthy skin supply is limited, demanding experiments such as this film seeded with autologous keratinocyte skin cells to repair a burned shoulder. Photo: Lyons Burn Centre, Edouard Herriot Hospital, Claude Bernard University, Lyons, France.

December 17, 2000 Madison, Wisconsin - In a week, it will be Christmas - a holiday to celebrate the birth of the man named Jesus Christ long considered by many to be divine, even immortal. The New Testament says his disciples heard Christ tell them that "whosoever believeth in Him who sent me shall have ever lasting life." As if to prove the lesson of his words, he also told the disciples that he would die before them and then resurrect with new life to walk among them again.

The Bible also describes Abraham and his bloodline that included Methuselah and Noah as living for centuries. In contrast, humans and most other earth creatures seem to have such short lives. Could life expectancy - even immortality - be a function of genetic sequencing on chromosomes?

Two important medical reports this month suggest that genome sequencing can extend life, and human skin might even be made immortal. Researchers at the University of Connecticut Health Center in Farmington have announced that the life span of fruit flies have been doubled when a gene was modified on a single chromosome. The senior author of the study, Dr. Stephen L. Helfand, said the gene mutation seems to work by restricting calorie absorption on the cellular level. Consequently, there is not as much weight gain, but the fruit flies' health and energy are normal. "By the time that 80-90% of normal flies are dead, these mutant flies are still doing just fine." Dr. Helfand thinks his research might be applied to developing a pill which could both extend human life and control weight.

Even more amazing is a completely accidental discovery of skin cells that do not die at the University of Wisconsin in Madison. In fact, Dr. Lynn Allen-Hoffmann - Professor of Pathology and director of the laboratory in which the cells reside -

calls them "immortal" - immortal human skin. When the miraculous cells were still alive and thriving after an entire year, instead of dying after a few weeks like normal skin, the University of Wisconsin Alumni Research Foundation patented the cells now known as "NIKS." That acronym stands for Near-Diploid Immortal Keratinocytes. The acronym also represents the lab's sense of humor. NIKS is SKIN spelled backwards.

It all started in early 1996 at the end of a research project in which Dr. Allen-Hoffmann and her lab assistants had been growing human skin cells in culture dishes over several weeks. In one set of dishes, she was testing a chemical additive on tissue. Another series of dishes had nothing added so she would have a normal control for comparison. Strangely, and still mystifying, one of the control dishes was different from all others.

Interview:

Lynn Allen-Hoffmann, Ph.D., Prof. of Pathology, University of Wisconsin Medical School, Madison, Wisconsin: "And it was in one of those control cell plates that my technician, Sandy Schlosser, noticed - and this was on the day we were literally going to fix, and by fix I mean formaldehyde-preserve these cells which would totally have terminated the experiment. Anything living in there would have been killed. We noticed there was a small colony of cells that had a phenotype that is called basal. They looked as if they were actively growing. They were small and very uniform in size and she came into my office and said, 'Lynn, come and take a look.'

And I went in and looked at this and she asked me what it was and I said, 'You know, that looks like an actively growing colony and this is very unusual. I don't know for sure what it is.' Why would that colony be living when clearly all the other cells in the dish were senescent?

WERE DEAD.

Were dead. And I recognized this was clearly unusual, so we had many replicate control dishes. So, I said, 'Go ahead and fix all the other plates in the experiment.' And she looked at all the other control dishes very carefully to see if there were any other colonies and there weren't. So, we just had that one plate and she put it back in the incubator.

And about a week or so later, we came back and it was quite clear that colony was growing and in fact, that colony produced enough cells to essentially cover the surface of that plate. And it was at that point in time that I recognized, 'This is quite unusual.'

I instructed her to cryo-preserve the cells every other week, or every other passage, so that we would generate a catalogue of these cells. She did that and she did that for a full year continuously! And after a year, we said, 'These cells by scientific definition had achieved immortality.' Because that is a very long time for this cell type to be living and actively growing at a consistent growth rate. And it did grow at a very consistent growth rate, identical to the parental cells from the tissue that we isolated the cells from initially. And I anticipated at first that these cells would be aberrant in some way in their characteristics

MEANING THEY MIGHT BE CELLS THAT WERE PRE-CANCEROUS OR HAD A DEFECT?

Yes. And so some of the first experiments we did was to have these cells at various passages karyotyped - that is, had their chromosomes analyzed to see if there were any large lesions or additions and whether the cells accumulated chromosomal abnormalities over this long period in cultures over the year. And we did indeed find that the cells had duplicated one section of the chromosome.

And that was chromosome 8 and it was a section of a long arm of chromosome 8. In looking at cells in different passages over the course of that year, we found an unusual thing and that was that the cells did not accumulate other growth chromosomal abnormalities and that the cells maintained this extra piece of chromosome 8. So, we hypothesized that this duplication of genetic material is important for the cells to have the immortal phenotype that they possess.

IN A NORMAL HEALTHY PERSON, WHAT WOULD CHROMOSOME 8 DO?

That is a complex question you just asked me, but suffice it to say that it is reasonable to speculate that the extra expression of genes that are coming from chromosome 8 perhaps play a role in the immortality that has happened to these cells. And does it confer other characteristics to the cells? That we have been investigating and we have stayed quite focused on characterizing the features of skin cells because this is what these cells are from, keratinocytes. They were derived from skin tissue keratinocytes that my lab studies and so we wanted to confirm that these cells are keratinocytes, which they are, and we are in the really fortunate position of having the infant's original foreskin cells with which to make comparisons to this cell line that has arisen from them. We are in a very unique position to be able to make that comparison and we have been making those comparisons.

And what was astounding to us was that this cell line that has this immortal growth characteristic is amazingly similar to the original parental cells. We were expecting to see some biochemical differences, some structural differences in the cells in culture, and we thus far have not observed that. We have looked to see if they exhibit any characteristics that would lead us to believe they are cancerous or pre-cancerous and the answer to that is no.

THEN THE NEXT STEP IS: COULD YOU PRODUCE LARGE QUANTITIES OF NORMAL HUMAN SKIN THAT COULD BE USED ON BURN VICTIMS?

Yes, and that is a really important question. We're doing animal grafting studies now with the NIKS cell graft to determine if we can indeed do that and if we can successfully get the cells grafted on to animal models. We have a lot of really exciting work to be done yet with regard to demonstrating that this will be a therapeutic value to the medical community. And we're excited about positioning ourselves so we can go forward with those types of experiments.

DO YOU THINK BASED ON THE WORK YOU'VE DONE SO FAR THAT THE IMMORTAL CELLS CAN BECOME A KIND OF INFINITE SUPPLY OF HUMAN TISSUE TO BE USED IN BURN VICTIMS?

That would be a dream come true. That would be a dream come true for a large number of people. One of the advantages of this cell line is that you don't have to harvest any more tissue. We have the cells. We know they don't carry viruses. They have been characterized to see if they contain viruses such as human papilloma virus which causes warts on our skin and also causes cervical cancer in women. NIKS cells do not possess that virus in that class. They don't possess the hepatitis virus. They don't possess HIV. So, this is wonderful! Or other pathogens we've tested for so far.

SO YOU'VE GOT A CLEAN LINE...

Clean, yes, for the things we've tested so far.

OF CELLS PERPETUATING HUMAN SKIN CELLS. AND SO THAT I'M CLEAR AND THE GENERAL AUDIENCE IS CLEAR, AFTER FIVE YEARS, YOU HAVE THE SAME STOCK OF THAT INFANT'S FORESKIN AND THOSE CELLS ARE NOT SHOWING ANY SIGNS OR INCLINATION OF DYING AS NORMAL HUMAN TISSUE WOULD....

Yes, that's right.

IF YOU CAN, AS YOU SAID, GENETICALLY ENGINEER THEM SO THEY WOULD GROW INTO MULTIPLE LAYERED NORMAL HUMAN SKIN THAT COULD BE USED IN BURN VICTIMS...

That would be terrific.

DOES THAT MEAN THAT SKIN GRAFTED ONTO A BURN VICTIM WOULD ALSO GROW FOREVER WITHOUT DYING AND THERE WOULD BE NO AGING AND NO WRINKLING?

(laughs) Well, that's a big question. I don't know. I don't know. I certainly wouldn't make those claims at this stage.

Let me tell you a little bit about this tissue and also another feature of the NIKS cells. A characteristic of our (human) skin is that the function it has is to die. And our skin is composed of many layers. And the upper layers of our skin, the layers that produce almost all the dust in your home, although people don't recognize this, each of us humans produce about 90 pounds of these skin cells in the course of our life. So, this skin is called 'renewal tissue.' And it constantly renews itself. It's a simple tissue but it's very elegant. And it's elegant because it protects us by the way in which the cells move and that movement is up from the regenerative layer of skin which is the first layer through the layers of skin and then mature skin cells called squamous are destined to fall off, to be knocked off our bodies by friction, by putting on and off clothing and so on.

Now, that directionality of cell movement is important because a lot of things that land on our skin - skin is our largest organ and its the organ most in contact with the environment - that pathogens such as viruses, bacteria, chemicals in the environment that land on our skin - even if they do penetrate our skin and they do, those cells are destined to fall off our body anyway. So, it's an elegant plan of nature for this organ to renew itself in that way.

What happens when our skin cells mature or go through a process called 'differentiation' is that they will lose the ability to replicate. In fact, they will totally lose their nucleus. So, that's something you can see histologically and you can see in a normal skin sample from you or me. When we cultured the NIKS cells in this organotypic culturing way which is different from a monolayer tissue culture in a Petri dish that we were talking about. In organotypic culturing, the cells are cultured in such a way that they will produce all the layers of skin, and the NIKS cells will also correctly produce all the layers of skin. That is the upper mixed cells will mature, lose their nucleus and fall off.

So, they can still obey the signals 'to die' when put in the correct tissue context. So that's why I was so excited!

WHAT ABOUT THE HUGE CONCERN OF SO MUCH OF THE POPULATION, ESPECIALLY IN THE WESTERN INDUSTRIALIZED WORLD, ABOUT WRINKLES AND AGING. ARE WE TREADING AROUND THE POSSIBILITY THAT THESE CELLS COULD ACTUALLY BE MADE TO CREATE SKIN THAT WOULD NOT DIE AND WOULD NOT WRINKLE?

(laughs) I guess I'm treading around it! I'm treading around it because as an academician I have not focused on that as a use of the cells. It is a distinct possibility though. It is a distinct possibility.

Another possibility is we don't know, because we haven't done the experiments yet, whether these cells can produce the appendages of skin. And what I mean by the appendages of skin is, for example, a hair. So, that's also another important experiment that we have not conducted yet to see if that is possible.

IF YOU WERE SPECULATING ON THE FUTURE FROM WHERE YOU'RE SITTING NOW AS A LABORATORY EXPERT, HOW LONG DO YOU THINK IT WOULD BE BEFORE YOU ACTUALLY HAVE COMMERCIAL PRODUCT THAT IS VIABLE IN MEDICINE AND PHARMACY AND COSMETICS?

This is a function of resources. And I think different groups who need to work together in order to understand the full potential of this technology. It could move quickly with the correct infusion of resources. I know at a minimum it will progress along. That's a hard question. You're asking someone who has a good sized lab at the Univ. of Wisconsin, but not a cast of hundreds. And who is getting a small private sector concern established with the aim of furthering development of the cell line for potential medical application and use in pharmacological screening. We're at the very early stages of this.

WOULD THE APPLICATION TO BURN VICTIMS PERHAPS BE ONE OF THE TOP PRIORITIES?

Well, that's certainly a very dramatic example of where there is a need. Certainly, the tools and products available to physicians are quite good, but currently there is not an intact skin equivalent that immediately can be placed on severely burned patients other than cadaver skin. I can anticipate a question you're going to ask me about immunological properties of NIKS cells and that's something we're working on right now.

COULD THEY GO ON TO ANYBODY?

I don't know. That would be great. We're working on this and you'll have to call me up in a year and interview me. I'll give you an update.

IF THERE IS NOT AN IMMUNOLOGICAL PROBLEM YOU CAN'T OVERCOME - THEN THESE CELLS COULD BECOME THE ANSWER TO BURN VICTIMS THROUGHOUT THE WORLD EVENTUALLY?

It is a distinct possibility."

More Information:

A new University of Wisconsin-Madison company called Stratatech, housed at University Research Park, is now pursuing markets for its patented "immortal human skin." One of its priorities is treatment for severe burn patients. At least 13,000 people are hospitalized for burns each year which require extensive skin grafting. Stratatech hopes to begin human trials of its NIKS skin by 2002. Another priority is cancer research. Stratatech's Director of Business Development is UW-Madison oncology professor, Michael Hoffmann, husband of Dr. Lynn Allen-Hoffmann.

Credits