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Improving the Revascularization of Transplanted Hair Follicles Through Up-Regulation of Angiogenic Growth Factors

Fabio Rinaldi, MD, Elisabetta Sorbellini, MD, Paola Bezzola, MD *Milan, Italy*

Hair follicles are avascular, like the interfollicular epidermis, and their growth is surrounded by perifollicular blood vessels arising from a deep plexus (the "fascial network") into subcutaneous adipose tissue and deep dermis. The capillary loops around the hair follicle nourish the hair bulb and dermal papilla cells through a rich blood supply.

Many studies have shown that hair growth depends on the induction of angiogenesis to meet the increased nutritional needs of the rapid cell division of hair follicle during the anagen phase, and that the number and diameter of perifollicular vessels significantly decrease during catagen and telogen (with more than fourfold reduction in perifollicular vessel size). It has been demonstrated that the hair follicle provides its own angiogenic stimulus, and that the angiogenic activities are related to the different phases of the hair cycle.

The real molecular mechanism of vascular control is not yet well known. Vascular endothelial growth factor (VEGF) plays an essential role in mediating angiogenesis during development of the hair cycle. VEGF enhances angiogenesis as well as microvascular permeability increasing the vessels' size during anagen. These changes coincide with the increasing size of hair follicles.

The enhancement of perifollicular vessels is mediated by the up-regulation of VEGF mRNA by cells of the dermal papilla and outer root sheath keratinocytes, with the consequent growth of hair follicles and hair shafts.

The hair growth depends also on the up-regulation of other growth factors such as fibroblast growth factor-7, insulin growth factor-1, and the direct stimulation of specific receptors of taurine and ornithine in the outer root sheath.

Transplanted hair follicles are avascular immediately after transplantation. One of the critical moments of hair transplantation can be the risk of an ischemia reperfusion injury of the hair grafts because of poor revascularization, and non-specific inflammatory response.

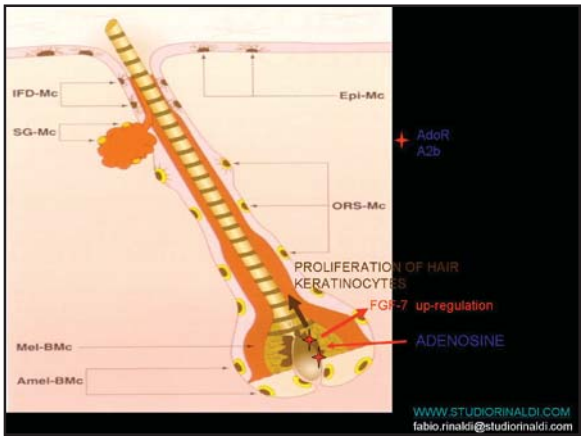

Figure 1. Adenosine sulphate directly stimulates the up-regulation of VEGF in dermal papilla cells *in vivo*, and the up-regulation of FGF-7 gene expression in DPC via specific receptor AdoR A2b.

Transplanted hair follicles must find the best condition in the scalp to start their life-long cyclic transformation. To survive, transplanted follicles need to avoid ischemia reperfusion injury, to meet the increased nutritional need to stimulate the rapid proliferation of follicular keratinocytes and the elongation and thickening of the hair shaft. Many of the transplanted hair follicles slip into the resting phase (telogen) before passing to the growth phase (anagen): active and resting follicles differ remarkably in the metabolism and control mechanism. Adachi *et al.* showed that in active follicles, compared with resting ones, glucose utilization is increased by 200%, glycolysis by 200%, activity of the pentose cycle by

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President's Message

Paul C. Cotterill, MD *Toronto, Ontario, Canada*


Paul C. Cotterill, MD

I was in Japan recently to participate at the ISHRS Asian Hair Surgery Workshop. At the end of the meeting, Dr. Kenichiro Imagawa, who did such a beautiful job of organizing the workshop, took the faculty on a very special 2-day tour of Kyoto and Nara, Japan. At one of the temples we visited, Dr. Imagawa pointed out a little-known fact, at least by the Western world. In Kyoto, there is a temple, established in 1150, that tells the story of what may be one of the very first transplants, even predating the work of Dr. Dieffenbach from Germany in 1822. According to the Shoren-in Temple's records, the temple was established in 1150 to protect the priests Honen and Shinran, who were developers of new Buddhist sects in the 13th Century. Contemporary followers of these sects regard the temple as a particularly sacred place. Dr. Imagawa tells me that the hair transplant story starts when Saint Shinran (1173–1262) entered the field of religion and shaved his hair in 1181. His mother saved the hair and implanted it on to a papier-mâché statue of Shinran and always kept it near her.

After she died, the papier-mâché statue was kept in the Shoren-in Temple for a long time.

Gradually, Saint Shinran's reputation was enhanced with more and more people wanting to worship the statue. As a result, the people of the temple made a wooden statue of Saint Shinran and put on a canonical robe, and transplanted his hair from the papier-mâché statue to his wooden statue and enshrined it near the temple or Annex, so everyone was able to worship it.

A believer built another temple in 1759 and worshiped three Amida divinities images with this statue by their side, which people called "Shoku Hatsu Do."

Now people pray at this temple or Annex for the purposes of "memorial services for scalp hair," "to have a large practice or prosperity," and "the advancement of the techniques." Dr. Imagawa tells me that these temples are especially good for people working as barbers and at hair salons. However, it wouldn't surprise me to see the odd hair restoration surgeon, now that word is out, making pilgrimages to the Shoren-in Temple to promote and grow their own practices.

During my trip to Japan for the regional workshop I also had the honor, along with Dr. Jim Arnold and his wife Betty, of having a very memorable dinner with the executive council of the Japanese Society of Clinical Hair Restoration (JSCHR): Drs. Takeshi T. Hirayama, Kuniyoshi Yagyu, Sotaro Kurata, Akio Sato, Yoshinori Ishii, and Tetuo Ezaki. Creating ties and friendships with members of local hair societies, such as the JSCHR, is a very important part of being able to reach out to interna-

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Drs. Wen-Yi Wu, Kenichiro Imagawa, Damkerng Pathomvanich, Jerry Wong, and Paul Cotterill are seen worshipping at the Shoren-in Hair Temple of Saint Shinran.

Co-Editors' Messages

Jerry E. Cooley, MD *Charlotte, North Carolina*


Jerry E. Cooley, MD

Where do we go from here? With our ability to densely transplant thousands of finely dissected follicular units, is there really much room for improvement until that day when cloning is here? In fact, I think the answer is yes and that we may be on the verge of a paradigm shift.

Paradigm shifts, according to Thomas Kuhn who coined the term, occur when "normal science" runs into "anomalies" that cannot be explained with the current way of thinking. The anomaly in our current paradigm is the variability in results we see among different patients. Why do some patients get better results if we do the same careful technique from case to case? Some of it, of course, is variability in hair characteristics, but that only explains some of it.

I'm not sure what this change in thinking should be called. Something to the effect of "wound healing and graft optimization." It would cover ideas and innovations such as new graft holding solutions, platelet rich plasma (PRP), hyperbaric oxygen, peri-operative use of low level laser therapy, and topical agents to promote angiogenesis. I'm not saying all of these ideas will ultimately prove useful. But I definitely think some of them will.

The current paradigm is that a structurally intact graft placed into an incision that doesn't stress the blood supply should in fact grow. In this model, grafting is a rather two-dimensional process. Emphasis on quantitative aspects of the process prevail: # of grafts, # of hairs, # of hairs/FU, # of grafts/cm^2, etc. The actual process of graft survival is a black box.

The new paradigm will certainly hold high respect for the intact graft and minimally disruptive incisions, but these will be seen as necessary but not sufficient for graft survival. The grafting process is viewed as a dynamic, organic three-dimensional process. Awareness of basic hair research and the surgical literature will inform this new view of hair transplantation. Graft survival will be seen as a small miracle that involves *ex vivo* storage, ischemia-reperfusion injury, passive oxygen absorption, and ultimately successful angiogenesis. It is patient "micro-variability" in these steps that explains the "macro-variability" in results in my opinion.

In this issue of the *Forum,* the new paradigm comes into our consciousness a little more. Rinaldi describes preliminary results with "Atodine," an agent that reportedly stimulates angiogenesis. It seems reasonable to me that anything that speeds up and augments the process whereby a new capillary network is established around our grafts would be beneficial.

Joseph Greco, PhD, describes his positive experience coating grafts with PRP as well as placing the gel into recipient sites and the donor area. In a personal communication, Greco told me that he recently saw two patients in whom PRP was used in their transplant 6 months prior. "My first impression was that they looked as though they were at 9 to 10 months rather than 6 months. The transplanted hair appeared more mature, with more aesthetic density than most patients do at that time." Of course, this is anecdotal data but from someone with as much as experience as Joe, I have to put some stock in that.

Jerry Cooley, MD

Robert S. Haber, MD *Cleveland, Ohio*


Robert S. Haber, MD

It has been a busy few months. Two weeks in Europe for the ESHRS and ISHR meetings, with a side trip to Dublin. One week vacationing with my kids. Ten days camping out West. And soon another week in New York City and more camping. More time out of the office for me than I've taken in years, and yet I don't seem at risk of declaring bankruptcy any time soon. How easy it is for us to put our lives outside of medicine on hold for "lack of time," knowing all the while how ever more precious that aspect of our lives becomes with time. I hope all of you have taken enough time for yourselves this summer.

Both the ESHRS meeting in Paris and the ISHR meeting in Milan were successful by any measure, and are fully covered elsewhere in this issue. Dr. Patrick Frechet organized a thorough didactic program and an incomparable social program that made us feel like royalty. There was also a live surgical program successfully beamed by satellite from Patrick's surgical center to the auditorium. I had the pleasure of demonstrating my Spreader during this program, but learned just before harvesting that my patient had undergone a scalp reduction just a month before. This can alter the vascularity of the donor area, and much to my consternation, the donor harvest was, shall I say, somewhat more sanguinous than desired while cameras were rolling. All turned out well though, and I enjoyed the subsequent opportunity to closely observe Drs. Ron Shapiro and Jerry Wong demonstrate their respective skills.

The ISHR meeting was organized by Dr. Vincenzo Gambino, and was well attended and very informative. The location was elegant, the meals were superb, and the gala dinner was one of the most special evenings ever, particularly for those who stayed until the wee hours.

In between, I visited with Dr. Maurice Collins in Dublin. Still relatively new to our field, he has many years of surgical experience, and has demonstrated himself to be meticulous, skilled, creative, and both gracious and generous. I feel fortunate to be able to consider him a friend.

As always, the recent meetings and office visit managed to bring new ideas into focus, and I've changed my practice yet again, always hoping to tweak my way to an elusive perfection.

As I now enter the crepuscule of my tenure as co-editor of the *Forum*, I begin to reflect on the concepts that have

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President's Message

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tional members and *potential* international members for the purposes of spreading the latest techniques in hair restoration, and also, as a by-product, through reaching out to these doctors with regional workshops and good relationships via the local societies, we can build and grow the membership of the ISHRS. Recently, the Italian Society of Hair Restoration (ISHR) also held its annual congress, hosted by Dr. Vincenzo Gambino, which was a great success. Next year in Rome there is an application to the ISHRS to have, for the first time, a joint ISHRS-Italian meeting hosted by Dott. Piero Schiavazzi of the Istituto Dermopatico dell'Immacolata (IDI) along with Dr. Ciro De Sio as the ISHR President as well as begin the Program Director with Dr. Bob Leonard. I am also delighted to report that Dr. Tommy Hwang has submitted an application to hold an ISHRS Regional Workshop in Seoul, Korea, next year. There is also further interest from international locations such as Mumbai, Tehran, Tokyo, and Sao Paulo.

The next Global Council meeting set for when the ISHRS meets in Las Vegas this September will be another chance for all the leaders of the local hair societies to sit down and discuss, among other things, the prospect of creating more regional workshops through the assistance of the ISHRS. I am very excited by this as I see the future success and growth of the ISHRS to be closely linked to the desire for our members to want to hold regional workshops, either on their own or in association with their local societies. If anyone else has this interest, please contact me and I will assist you in submitting an application.

Paul C. Cotterill, MD
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Haber Message

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appeared within its pages over the past few years, and how they have changed me. I value the *Forum* partly for its permanence and luxury of time it grants for learning. While concepts conveyed in a 7-minute presentation or great ideas fleetingly discussed in a hallway do not always "take root," I can take time to absorb the ideas in an article and refer back to it as often as needed. I do hope the *Forum* is as gratifying for you to read as it is to create.

Bob Haber, MD

Guidelines for Submitting an Article to the Forum

- ✓ Send submission *AND* Author Consent Release Form electronically via e-mail to Robert Haber, MD, at HaberForum@aol.com
- ✓ Include all photos and figures referred to in your article as separate attachments in JPEG, TIFF, or BMP format. Be sure to attach your files to your e-mail. Do *NOT* embed your files in the e-mail itself.
- ✓ An Author Consent Release Form must accompany your submission. The form can be obtained in the Members Only section of the website at www.ishrs.org.
- ✓ Financial conflicts of interest with devices, pharmaceuticals, cosmeceuticals, etc. discussed in your paper must be disclosed at the beginning of your submission.
- ✓ Trademarked names should not be used to refer to devices or techniques, when possible.

Submission deadlines: June 10 for July/August issue; August 10, September/October; October 10, November/December