

Extra View

# The Pluripotency of Hair Follicle Stem Cells

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Received 12/09/05; Accepted 12/09/05

Previously published online as a Cell Cycle E-publication:

<http://www.landesbioscience.com/journals/cc/abstract.php?id=2397>

## KEY WORDS

hair follicle, bulge area, stem cell, green fluorescent protein, nestin, differentiation, neuron, glial cell, nerve regeneration

## ABSTRACT

The hair follicle bulge area is an abundant, easily accessible source of actively growing, pluripotent adult stem cells. Nestin, a protein marker for neural stem cells, is also expressed in follicle stem cells as well as their immediate differentiated progeny. The nestin-expressing hair follicle stem cells differentiated into neurons, glial cells, keratinocytes and smooth muscle cells in vitro. Hair-follicle stem cells were implanted into the gap region of a severed sciatic nerve. The hair follicle stem cells greatly enhanced the rate of nerve regeneration and the restoration of nerve function. The follicle stem cells transdifferentiated largely into Schwann cells which are known to support neuron regrowth. Function of the rejoined sciatic nerve was measured by contraction of the gastrocnemius muscle upon electrical stimulation. After severing the tibial nerve and subsequent transplantation of hair-follicle stem cells, the transplanted mice recovered the ability to walk normally. These results suggest that hair-follicle stem cells provide an important accessible, autologous source of adult stem cells for regenerative medicine.

The hair follicle cycles throughout the lifetime of mammals, going through a growth phase (anagen), regression phase (catagen), and a resting phase (telogen).<sup>1</sup> In each cycle, the hair follicle goes through a period of growth, senescence, and eventual rejuvenation. Therefore, the stem cells of the hair follicle must be active especially in the time the hair follicle is regenerated.

The hair follicle stem cells were identified by Cotsarelis et al.<sup>2,3</sup> to reside in the bulge area of the hair follicle near the sebaceous gland. Subsequent studies have shown that these stem cells could not only produce the hair follicle but could regenerate or at least heal wounds in the epidermis.<sup>4-6</sup> These studies hinted at the potential pluripotency of the hair follicle stem cells.

In 2003, Li et al.<sup>7</sup> made a fundamental observation that the hair follicle stem cells may be highly pluripotent. Li et al. observed in transgenic mice in which a regulatory element of nestin drives GFP (ND-GFP) that nestin, a neural stem cell marker, was expressed in both neural stem cells and hair follicle stem cells. This observation suggested that hair follicle stem cells could be converted into neurons. The nestin-expressing stem cells found in the bulge area of the hair follicles were shown to be true hair follicle stem cells in that they were observed to form the outer and inner route sheath of the hair follicle during anagen.

Subsequently, Amoh et al.<sup>8</sup> observed that in culture the ND-GFP hair follicle stem cells could be converted into neurospheres, which in turn, formed neurons, glial cells, keratinocytes, smooth muscle cells, and other cell types. When the ND-GFP hair follicle stem cells were injected subcutaneously in mice, they formed neurons. Amoh et al.<sup>9</sup> also observed that when the ND-GFP hair follicle itself was transplanted to mice, the bulge area of the hair follicle gave rise to blood vessels indicating the potential of the hair follicle stem cells to form endothelial cells.

The results described above suggested that the hair follicle stem cells could be used for therapeutic purposes for what is now called regenerative medicine. Amoh et al.<sup>10</sup> have subsequently shown that when the hair follicle stem cells are cultured and then injected into an area between the fragments of a severed sciatic or tibular nerves, the nerves regenerated. The mechanism of regeneration seemed to be due to differentiation of Schwann cells from the hair follicle stem cells which formed myelin sheaths around the axons promoting axonal growth and the rejoining of nerves. When tested for function, the rejoined nerves were able to stimulate muscle contraction and enable the mice to walk normally again.

These results demonstrate the pluripotency of hair follicle stem cells and their potential use in regenerative medicine. The hair follicle stem cells may become the stem cells of choice in the future for regenerative medicine, since (1) they are readily available from essentially anyone, (2) they are easily cultured and expanded, (3) they are highly pluripotent, (4) they have been demonstrated to be able to support the regrowth of nerves, (5) they do not carry the ethical issues that embryonic stem cells and fetal stem cells do.

The near future should be an exciting time in stem cell research in which the true potential of the hair follicle stem cells for regenerative medicine can be determined. Exciting applications include regeneration of the injured or severed spinal cord, neurological diseases such as Parkinson's and Alzheimers as well as applications to other organs including the pancreas for diabetes and the liver for many types of diseases.

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