Despite its tiny size, the hair follicle (HF) is a complex organ that can regulate its cyclic growth and regression processes in a largely autonomous fashion through close communication between its epithelial and mesenchymal components [9, 47]. Hair research and pharmacologic intervention therefore focus mainly on local regulatory circuits, such as HF testosterone metabolism or growth-factor-activated pathways [16, 46]. Beyond its autonomous regulation of growth and regression however, the HF is located in an environment rich in structures and cells that connect local to systemic regulatory systems, such as the endocrine (Chap. 2) and the nervous and immune systems (Fig. 3.1) [20, 34, 39, 40]. Interaction of these systems with the HF and with each other leads to a strong impact on hair growth behavior.

Neuronal mediators such as the sensory neuropeptide substance P (SP), for example, can turn on or terminate hair growth control mechanisms, such as keratinocyte proliferation or neurogenic inflammation.
associated with HF regression [35, 39, 40]. At the same
time, growth factors excreted by HF cells, such as the
neurotrophin nerve growth factor (NGF), modulate the
structure and function of their environment through,
for example, perifollicular innervation, intra- and peri-
follicular immune cell populations, and neuroimmune
communication [13, 37, 43].

In short, the HF and its local regulatory circuits de-
pend on systemic mechanisms that can override local
hair growth regulation and therefore they deserve close
scrutiny, scientific appreciation, and pharmacologic tar-
geting. Throughout this chapter we will focus on the HF
as a model organ defined by lifelong plasticity of the ac-
companying immune cell populations and perifollicu-
lar innervation. This model may serve as an instructive
blue-print for the analysis and understanding of neuro-
immune regulation in epithelial tissue remodeling pro-
cesses.

Fig. 3.1 The hair follicle is a target for systemic regulatory
mechanisms involving the immune and nervous systems.
This schematic figure depicts the hair follicle as an exemplary
neuroimmune–mesenchymal–epithelial interaction system at
the point between challenges and adaptive mechanisms.

3.2 History

Our knowledge of the HF as a target for cutaneous nerve
fibers and immune cells reaches back to the time when
techniques to detect nerve fibers and immune cells in
situ became available a century ago. Modern research
approaches, in particular the development of trans-
genetic mouse models and great advances in immunohis-
tochemistry and molecular biology, have helped in the
identification of a large array of candidates responsible
for mediating pilo–neural–immuno interactions [14,
31, 39]. However, William Montagna's statement in his
famous book The Structure and Function of Skin more
than 30 years ago still holds true today:

“The largest sense organ of the body, interposed
between the organism and its environment, skin must
maintain that organism in a constant state of awareness
of all environmental changes. ... Yet precious few of the
problems that involve cutaneous innervation and spe-
cific cutaneous sensibilities have been solved, let alone
the clinical problems that are in some way related to the
peripheral nervous system.”

Since the early 1990s, however, interdisciplinary
research focusing on the nervous system and its inter-
action with the immune system has been constantly
producing new perspectives and insights into neuroim-
mune regulatory mechanisms in healthy and diseased
skin, many of which apply to hair growth.

3.3 Neuro–Immuno–Epithelial
Interactions in Normal
and Pathological Hair Growth

The HF is a densely innervated skin appendage, and re-
lationships between the HF and its innervation are truly
bi-directional: while neuromediators and neuropeptides
are capable of influencing hair growth, HF keratino-
cytes produce NGF and other neurotrophic factors and
induce remodeling of skin innervation in a hair-cycle-
dependent manner [13]. The same is true for interac-
tions between the HF and immune cells located nearby
in the dermis and subcutaneous tissue. Keratinocytes in
“healthy” HF's for example are protected from an attack
by immune cells by their “immune privilege” character-
ized by low levels of major histocompatibility complex
(MHC) class I/II antigens [33]. Below, we briefly sum-
marize our current knowledge on the neuro–immuno–
epithelial interactions during the normal hair cycle, as
well as in a number of pathological skin conditions,
such as the stress response and autoimmune hair loss
[alopecia areata (AA)].