Journal of Dermatological Science 69 (2013) 6–29

Contents lists available at SciVerse ScienceDirect

Journal of Dermatological Science

journal homepage: www.elsevier.com/jds

Invited Review Article

Mutant laboratory mice with abnormalities in hair follicle morphogenesis, cycling, and/or structure: An update

Motonobu Nakamura [a,*], Marlon R. Schneider [b], Ruth Schmidt-Ullrich [c], Ralf Paus [d,e]

[a] Department of Dermatology, University of Occupational and Environmental Health, Kitakyushu, Japan
[b] Institute of Molecular Animal Breeding and Biotechnology, Gene Center, LMU Munich, Munich, Germany
[c] Max-Delbrück-Center, Berlin, Germany
[d] Department of Dermatology, University of Luebeck, Luebeck, Germany
[e] Institute of Inflammation and Repair, University of Manchester, Manchester, UK

ARTICLE INFO

Article history:
Received 30 August 2012
Received in revised form 2 October 2012
Accepted 4 October 2012

Keywords:
Hair follicle morphogenesis
Hair cycle
Knockout
Mouse
Transgenic

ABSTRACT

Human hair disorders comprise a number of different types of alopecia, atrichia, hypotrichosis, distinct hair shaft disorders as well as hirsutism and hypertrichosis. Their causes vary from genodermatoses (e.g. hypotrichoses) via immunological disorders (e.g. alopecia areata, autoimmune cicatrical alopecias) to hormone-dependent abnormalities (e.g. androgenetic alopecia). A large number of spontaneous mouse mutants and genetically engineered mice develop abnormalities in hair follicle morphogenesis, cycling, and/or hair shaft formation, whose analysis has proven invaluable to define the molecular regulation of hair growth, ranging from hair follicle development, and cycling to hair shaft formation and stem cell biology. Also, the accumulating reports on hair phenotypes of mouse strains provide important pointers to better understand the molecular mechanisms underlying human hair growth disorders. Since numerous new mouse mutants with a hair phenotype have been reported since the publication of our earlier review on this matter a decade ago, we present here an updated, tabulated mini-review. The updated annotated tables list a wide selection of mouse mutants with hair *growth* abnormalities, classified into four categories: Mutations that affect hair follicle (1) morphogenesis, (2) cycling, (3) structure, and (4) mutations that induce extrafollicular events (for example immune system defects) resulting in secondary hair growth abnormalities. This synthesis is intended to provide a useful source of reference when studying the molecular controls of hair follicle growth and differentiation, and whenever the hair phenotypes of a newly generated mouse mutant need to be compared with existing ones.

Contents

Abbreviations: ENU, ethyl-nitrosourea induced chemical mutagenesis; GEMs, genetically engineered mice; HF, hair follicle; Rad, radiation induced; S, spontaneous mutation; Tg, transgenic; TGF, transforming growth factor; Tm, targeted mutation.

* Corresponding author at: Department of Dermatology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. Tel.: +81 93 691 7445; fax: +81 93 691 0907.
E-mail address: motonaka@med.uoeh-u.ac.jp (M. Nakamura).

0923-1811/$36.00
http://dx.doi.org/10.1016/j.jdermsci.2012.10.001

1. Introduction

Over the past two decades, the molecular controls that drive hair follicle (HF) development and cycling have become one of the most intensively investigated and productive areas of skin research. Here, fundamentally important controls that range from mechanisms of organ induction and morphogenesis via principles of stem cell and pigmentation biology, topobiology, cell commitment, differentiation, and programmed death to complex cell-cell and tissue interactions can be studied exemplarily in a model mini-organ [1,2]. As such, the study of hair growth phenomena and of mutations associated with hair phenotype changes has permitted novel insights into general biological principles that extend far beyond skin and hair research.

Moreover, the study of hair phenotypes in spontaneous mouse mutants or genetically engineered mice (GEM) with precisely defined lack-of-function or gain-of-function mutations has provided invaluable mechanistic insights into the – as yet often unknown or ill-understood – causes of human hair growth disorders. The range from genodermatoses (e.g. papular atrichia, monilithrex, hypotrichosis simplex) via immunological disorders (e.g. alopecia areata, autoimmune cicatrical alopecias) to hormone-dependent abnormalities (e.g. androgenetic alopecia). While caution is advised to avoid oversimplistic equations between animal models and human hair disease, mutant mice certainly offer excellent clues to specific disease mechanisms, which can be followed-up in the human system. Mouse mutants with a hair phenotype are therefore an invaluable tool for improving our often very limited understanding of human hair pathology, and are likely to generate important new insights into the molecular basis of different types of alopecia, atrichia, hypotrichosis, hair shaft disorders, hirsutism and hypertrichosis.

The current mini-review is presented mainly in the form of annotated tables, and constitutes an update of earlier tabulated review that we had published more than a decade ago [3]. Numerous novel mouse mutants with a hair phenotype have been published since, justifying an extensive up-date. The present, updated tables list a wide selection of mouse mutants with hair *growth* abnormalities, while mutants in which the primary phenotype abnormalities lie in hair pigmentation or in the sebaceous gland were omitted. The mouse mutants with a hair phenotype presented here have been classified into four categories: mutations that affect HF (1) morphogenesis, (2) cycling, (3) structure, and (4) mutations that induce extrafollicular events, for example immune system defects, resulting in secondary hair growth abnormalities. These updated tables also should facilitate comparisons between the hair phenotype of a newly generated mouse mutant with existing ones.

2. Analysis of hair follicle morphogenesis and cycling: the importance of professionally executed, quantitative histomorphometry

HF morphogenesis is focally initiated via an inductive signaling exchange between epidermal keratinocytes which eventually adopt a HF fate, and a specialized population of dermal fibroblasts, which at first form the dermal condensate and at later stages the follicular dermal papilla (DP) [1]. This bi-directional epithelial-mesenchymal interaction is governed by a tightly controlled balance between numerous growth stimulators and inhibitors, which drive the developing HF through defined, genetically programmed series of morphogenetic stages that culminate in the formation of a fiber-producing mini-organ [2].

Once HF morphogenesis is completed, the HF continuously undergoes regular cycles of regeneration coupled with an extremely high proliferation and protein synthesis activity (anagen), followed by an apoptosis-driven organ involution (catagen) and a relative resting phase (telogen) [1,2]. Similar to HF development, HF cycling is governed by signaling interactions between the dermal papilla cells and HF keratinocytes. Numerous soluble factors, transcription factors and adhesion molecules play indispensable roles in these signaling interactions.

While, in contrast to human HFs, hair shaft shedding (exogen) in mice is an actively regulated process, the old hair shafts from preceding cycles are often retained by healthy murine HFs, at least during the first few cycles [4,5]. Therefore in mice even substantial abnormalities of HF cycling are not necessarily associated with substantial hair loss (alopecia), and can easily be missed, if quantitative hair cycle histomorphometry is not performed (see below).

Using comprehensive guides for recognition and classification of distinct stages of murine HF morphogenesis [6] and hair cycling [7], it has become easier to compare mutant with control mice. However, four routine mistakes frequently obstruct a professional hair phenotype analysis of mutant mice:

1) Investigators tend to erroneously equate HF morphogenesis with what they consider to represent the "first hair cycle". These investigators ignore that HF morphogenesis in mice continues well into the first week of postnatal life and is only terminated by the induction of HF cycling when the HF first enters catagen between P17 and P19. As HFs which are still undergoing development are biologically distinct entities from mature, cycling HFs, this can lead to erroneous assumptions and ill-founded hypotheses. Thus, postnatal HF morphogenesis and HF cycling must be carefully distinguished, and should be analyzed separately (for details, see Sections 5–7).
2) Hair growth phenotype analysis is often performed only on the basis of very limited qualitative comparisons between age-matched mutant and wild type mice. This tends to both overinterpret and overlook phenotypic abnormalities. Therefore, a fully quantitative assessment of HF morphogenesis and cycling, which can be complemented with a "hair morphogenesis score" (HMS) and a "hair cycle score" (HCS), is mandatory for a professional hair phenotype analysis (details, Sections 5–7).
3) Murine HFs come in several important anatomical varieties with distinct structural characteristics: vibrissae HFs, and guard HFs (syn. Tylotrich HFs), auchenne, awl and zigzag pelage HFs [4]. The development of these functionally and structurally distinct HF subpopulations is induced at different time points of fetal, perinatal, and/or postnatal life, and their molecular controls can differ substantially. Thus indiscriminately lumping together these distinct HF subpopulations during hair phenotype analysis is both inaccurate and inappropriate. This obscures important molecular pathobiology clues that a separate analysis of individual HF sub-types would have revealed otherwise.
4) Distinct pelage HF subpopulations begin to develop in waves in defined skin regions, and then go on to cycle in well-synchronized waves, which finally break-up into isolated cycling domains that subsequently become ever-more heterogeneous with progressing age of the mouse. Therefore, it is absolutely critical for professional hair phenotype analyses to not only carefully age-match mutant mice with WT controls – ideally gender-matched littermates – but also to only compare standardized identical reference areas of pelage hair.

If these frequent mistakes are avoided, the hair phenotype analyses of loss-of-function and gain-of-function mice will further deepen our understanding of the functional roles of the mutated proteins in skin and hair biology, and will offer invaluable pointers to mechanisms underlying comparable human hair diseases.