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Fifty years of the asebia mouse: origins, insights and contemporary developments

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Abstract: First described as an alopecic spontaneous mutant mouse line lacking sebaceous glands in a publication in *Science* in 1965 by Allen H. Gates and Marvin Karasek, asebia mice soon became a popular tool for rodent sebaceous gland research. In addition to the study of sebaceous lipids, the original asebia mice and subsequent allelic mutations were widely employed to examine the influence of the sebaceous gland on hair growth, epidermal proliferation, dermal inflammation and skin carcinogenesis, among other aspects. With the identification of *Scd1* gene mutations as the genetic basis of the asebia phenotype and with the advent of more refined methods for manipulating the mouse genome, asebia mice progressively lost importance. However, they contributed to, or even provided the initial spark for, several current research topics. These include the role of the sebaceous gland in hair shaft–sheath interaction and its significance for cicatricial alopecia, and the antimicrobial activity of sebum. Furthermore, mice with skin-specific deletion of SCD1, which have increased energy expenditure and are protected from high fat diet-induced obesity, provided novel insights into the crosstalk between the skin and peripheral tissues in maintaining energy homeostasis. In briefly reviewing its story, this commentary pays tribute to asebia mice and to the original publication in its golden anniversary year.

Key words: alopecia – asebia – mice – sebaceous gland – skin

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Spontaneous mouse mutations have been studied for decades to identify the molecular basis and the pathophysiology of diseases and to test novel therapeutic strategies. As defects of skin and hair are readily apparent to animal caretakers, a large number of mutations relevant for dermatological research became available as a by-product of mouse breeding. Nonetheless, the new mutant mouse line with progressive alopecia reported by Gates and Karasek in 1965 (1) caused some sensation because the key histological abnormality was the absence of the sebaceous glands (SGs). The (then unidentified) gene was named asebia, meaning 'without sebum', and the gene symbol *ab* adopted to symbolize the mutation. The name asebia has been retained until this day, notwithstanding the discovery that hypoplastic SGs are present in the skin of these mice.

Gates and Karasek's classical paper in brief

In their succinct report (the full text is freely available via http://www.sciencemag.org/content/148/3676/1471.long), Gates and Karasek (1) initially describe the appearance of a new mutant line in a BALB/cCrglGa mouse colony displaying impaired coat growth detectable from 7 to 9 days of age.

Other features include the presence of scales among the sparse hair and signs of eye inflammation leading to blindness in older animals. Mutant mice also showed impaired weight gain and reduced fertility, which are indeed a common feature of alopecic mice. Test breeding revealed that the condition is due to an autosomal recessive mutation with complete penetrance. Histologically, the authors report the complete absence of SGs, hyperkeratosis and a somewhat 'excessive development' of hair follicles, which extend deep into the fat tissue and are frequently plugged with keratotic material. Reciprocal skin transplantation between normal and mutant mice revealed a partial rescue of the phenotype and suggested that some soluble substance synthesized by the normal skin may alleviate the changes in the mutant skin.

Further characterization and uses of the asebia mouse

Detailed study of the histological features of the *ab* skin revealed that SGs initially develop normally in these mice, but the characteristic lipid accumulation leading to holocrine secretion is impaired (2). Thus, SGs are hypoplastic rather than aplastic, and easily overlooked. Among the modified SGs, only the meibomian glands are considerably affected (2). Other changes include moderate epidermal and dermal thickening, the presence of morphologically abnormal fibroblasts, alterations in collagen and elastin and increased dermal vascularization and inflammation (3). Hair follicles show delayed cycling and extend deep into the dermal adipose tissue, and the hair canal is frequently plugged with cells of the inner root sheath that adhered to the hair shaft (4). The spontaneous mutations ab^{J} (5) and ab^{2J} (6), identified at the Jackson Laboratory in 1968 and 1993, respectively, revealed to be allelic to *ab*, showed equivalent histological features, and were frequently employed in further studies.

The most obvious initial application of asebia mice was the analysis of skin lipids, and *ab* skin was shown to be deficient in esterified sterol and waxes, but overproportionally rich in free sterols, suggesting a fundamental defect in fatty acid metabolism in the epidermis (7). In addition, asebia mice were later employed to study the hyperproliferative phenotype and to assess the effects of antiproliferative drugs (8), but they turned out to be a limited psoriasis model. Furthermore, asebia mice have been employed to study skin carcinogenesis (9), dermal inflammation (10) and parasite skin penetration (11).

Identification of a Scd1 mutation as the molecular basis of the asebia phenotype and further developments

The genetic basis of the asebia mutation was elucidated in 1999 with the identification of genomic deletions of *Scd1*, a gene encoding the enzyme stearoyl-CoA desaturase 1, in ab^{J} and ab^{2J} mice (12). SCD1 is a rate-limiting enzyme in the synthesis of monounsaturated fatty acids, and a member of the SCD family (13). *Scd1* mutations were further confirmed as the source of the asebia phenotype by *Scd1* targeting mutations (14,15). In addition, these and subsequent mouse lines carrying tissue-specific *Scd1* mutations provided novel and unexpected information about the role of SCD1 in whole-body energy balance. Notably, skin-specific *Scd1* deletion resulted in increased whole-body energy expenditure, protection against diet-induced adiposity, hepatic steatosis and glucose intolerance, thus linking cutaneous lipid metabolism to whole-body energy balance (16).

Since the identification of *Scd1* mutations as the basis for the asebia phenotype, additional spontaneous (17) and mutagen-induced (18) *Scd1* mutations mimicking the asebia phenotype have been reported. The latter mutant, originally termed flake, show impaired clearance of skin infections by gram-positive bacteria, suggesting the presence of a sebaceous lipid-based antimicrobial pathway in mammalian skin (18).

Legacy and perspectives

The major merit of asebia mice was to draw the attention of researchers to a rather neglected skin structure, the SG. They stimulated the examination of the composition and function of sebaceous lipids and of the role played by the SG in hair growth and regeneration, now an area of intense research (19–22). Indeed, careful histopathological studies of asebia skin showed that in the absence of SGs, separation of the hair shaft from the sheath is impaired, which prevents shaft exit and leads to follicle destruction similarly to that observed in human cicatricial alopecia patients (4,6). Therefore, the SG is not simply a source of sebum, but its physical presence seems to be necessary for normal hair shaft–sheath interaction. This important nuance is supported by previous *in vitro* studies employing human, sheep or horse hair follicles (23,24). Consequently, clarifying the importance of sebum for hair growth and cycling, and of the role played by sebum in mouse skin physiology in general, awaits the development of a model in which sebum production is impaired, while the structural properties of the SG are maintained.

Conflict of interests

The authors have declared no conflicting interests.

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