At their first studies on the physiology and pathophysiology of the skin looking for an adequate field of future dedication, budding skin researchers usually go quickly through the chapter on the Biology of Sebaceous Glands having obtained the following piece of knowledge: sebaceous glands produce sebum and are partially responsible for acne vulgaris. Seemingly, a limited and less attractive field to work in, as Albert M. Kligman already pointed out in 1963 with his statement “The sebaceous gland is a living fossa with a past but not future,” in Montagnas’ Advances in Biology of the Skin.

Therefore, it may be of major importance for dermatological research that a small number of dedicated researchers have made a silent revolution during the last two decades by revising the role of the sebaceous gland in human skin. This skin appendage has turned to be an organelle with major involvement in skin homeostasis, since sebaceous lipids fractions have been shown to be responsible for the three-dimensional organization of the skin surface lipids and the integrity of the skin barrier (Pilgram et al., 2001; Fluhr et al. in press), and sebum was found to transport antioxidants to the skin surface (Thiele et al., 1999). In addition, sebaceous platelet-activating factor acetylhydrolase II was found to protect the skin against oxidative stress and, especially, epidermal keratinocytes against ultraviolet B irradiation (Marques et al., 2002), the sebum-specific lipids (C16 : 1Δ6) to exhibit innate antimicrobial activity (Ge et al. in press; Wille and Kydonieus, in press), and sebocytes to express pro- and anti-inflammatory properties (Zouboulis et al., 1998; Böhm et al., 2002; Toyoda et al., 2002; Wröbel et al., 2003), to present a regulatory program for neuropeptides to the skin surface (Thiele et al., 1999). In addition, sebaceous gland functions were currently under investigation (Zouboulis et al., 1998; Chen et al., in press) How much has changed since 1963!

In this issue, Thiboutot and colleagues put another milestone to the sebaceous revolution. Based on previous knowledge that sebaceous glands are capable of synthesizing cholesterol de novo from acetate (Cassidy et al., 1986), they investigated whether the skin, and especially the sebaceous gland, is capable of utilizing cholesterol as a substrate for steroidogenesis. Cholesterol is used in cell membrane construction and is a lipid fraction of sebum, but its utilization by the skin as a substrate for steroidogenesis would fulfill an important requirement for the skin function as an independent peripheral endocrine organ (Zouboulis et al., 2000). In order for steroid synthesis to occur, cholesterol needs to be transported from the outer root to the inner mitochondrial membrane and consequently be converted into pregnenolone via the P450 side chain cleavage enzyme in concert with its cofactors adrenodoxin, adrenodoxin reductase, and the transcription factor steroidogenic factor-1. Pregnenolone is converted to 17-hydroxypregnenolone via 17α-hydroxylase and to the androgen precursor dehydroepiandrosterone by 17,20-lyase. 17α-Hydroxylase and 17,20-lyase activities are catalyzed by P450c17. Thiboutot and colleagues have shown that all enzymes required for utilizing cholesterol as a substrate for steroidogenesis are present in human sebocytes with P450 side chain cleavage enzyme, adrenodoxin reductase, and P450c17 expressed in the cytoplasm, whereas steroidogenic factor-1 exhibited perinuclear or nuclear localization. In addition, they found that sebocytes converted 22-hydroxycholesterol to 17-hydroxypregnenolone. These results, together with previous data suggesting a major role of sebocytes in the conversion of dehydroepiandrosterone to the potent androgens testosterone and 5α-dihydrotestosterone (Thiboutot et al., 1995, 1998; Chen et al., 1998; Fritsch et al., 2001), indicate that the skin is, indeed, a steroidogenic tissue to be added to the list including the classical ones, adrenal gland and gonads, as well as placenta, brain, and intestine. Moreover, the responsible skin compartment for both the initiation of steroidogenesis and the local production of potent androgens seems to be the sebaceous gland.

This wealth of new fascinating data would not be acquired without the existence of adequate experimental models. Since sebaceous gland differentiation is extremely species-specific, human models are required. After the less successful efforts by Kellum (1966) and Karasek and Charlton (1977) to develop models for the investigation of the human sebaceous glands, Kealey et al. (1996) and Xia et al. (1989) introduced the maintenance of the sebaceous gland ex vivo and the cultivation of sebaceous gland cells in vitro, respectively (reviewed in Zouboulis et al., 1999, 2001). Sev- eral modifications of the technique of Xia et al. (1989) have facilitated the reproducible cultivation of human sebocytes in vitro. However, human sebocytes are predisposed to differentiate by accumulating neutral fat droplets until they burst and die. Therefore, adequate cell amounts for large scale experiments can only be obtained from multiple donors, while prolonged experiments are hindered by the short life span of the cells. To overcome this problem, Zouboulis et al. (1999) transfected human facial sebocytes with Simian Virus-40 large T antigen and immortalized them. The resulting patented cell line, termed SZ95, has been cloned and further investigated, was shown to retain major characteristics of normal human sebocytes, such as differentiation with increase of cell volume and lipid synthesis and subsequent apoptosis, expression of characteristic origin- and function-specific proteins of human sebaceous glands, and expected biological response to androgens and retinoids (Zouboulis et al., 1999; Wröbel et al., 2003), and has been widely used in skin research since then.

To perform their experiments, Thiboutot and colleagues have applied the transfection system used by Zouboulis et al. (1999) to develop a second immortalized human facial sebaceous gland cell line, termed SEB-1. Like SZ95 sebocytes, SEB-1 sebocytes also express characteristic sebaceous gland proteins and their cytoplas- m induces oil red O stain-positive lipid droplets. In gene array studies, genes characteristic of sebaceous glands and those involved in lipid and steroid metabolism were expressed in SEB-1 sebocytes. The results by Thiboutot and colleagues confirm the findings by Zouboulis et al. (1999) that human
immortalized sebocytes transfected with Simian Virus–40 large T antigen possess normal sebocyte properties despite their immortalization. An explanation for this finding could be the progressed stage specific epithelial differentiation of the parental normal sebocytes which may hinder differentiation of the cells following their transfection.

Immortalized human facial sebaceous gland cell lines contribute significantly to the ongoing revision of the role of the human sebaceous gland towards a major contributor in skin homeostasis. Moreover, they will markedly assist the continuous advancement in our understanding of skin endocrinology as well as the intensification of investigations on the involvement of the sebaceous gland in skin diseases. The sebaceous gland and the research on it have a fantastic future!

REFERENCES


