12 The Psoriasis SCID Mouse Model: A Tool for Drug Discovery?

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12.1 Modeling Psoriasis

12.1.1 Definition of the Disease

Psoriasis is a common inflammatory skin disease affecting about 2% of the population in the Western world. Its prevalence along with a chronic recurrent course turns it into a significant socioeconomic problem. The basic features of its pathogenesis have long been recognized and are readily reflected by the characteristic clinical phenotype of the most common variant, chronic plaque-stage psoriasis: Affected skin areas are erythematous and elevated because of a dense inflammatory infiltrate. The resulting plaques are covered by a silv-
ery scaling reflecting the excessive hyperproliferation of the keratinocytes. To date, there is broad consensus that inflammation precedes the epidermal changes, but the occurrence of inflammation and epidermal hyperproliferation are the hallmarks of psoriasis.

Histologically, both processes can be described in more detail. Elongated and dilated capillary loops in the dermal papillae mirror a state of increased angiogenesis, with the endothelial cells in the affected areas expressing adhesion molecules of the selectin class. The latter initiate the multistep process of leukocyte extravasation, a prerequisite in the formation of an inflammatory infiltrate, which is located in the upper dermis; but cells also invade the epidermis’ neighboring areas of papillary dermis with the enlarged capillary loops. Lymphocytes contribute significantly to this infiltrate with T-helper cells being evenly distributed, whereas T-suppressor cells show a bias towards epidermal localization. Epidermal hyperproliferation results in profound epidermal thickening (acanthosis) and expanded epidermal rete pegs into papillary dermal space (papillomatosis). The turnover rate of epidermal cells is dramatically accelerated, resulting in faulty keratinocyte differentiation: The granular layer is constantly absent over the tips of the dermal papillae, and persisting nuclei of keratinocytes sometimes occur in the corneal layer (parakeratosis).

The complex phenotype of psoriasis is influenced by multiple factors, and there is ample evidence for several genes contributing to its genetic background.

By definition, a model system is a simplified representation of reality allowing more controlled manipulations of defined parameters. From a scientific point of view, a model is intriguing, if it is simple. Therefore, studies in cell culture systems seem more informative than those in complex systems, e.g., animal models. The opposite is often true in the field of applied biomedical research, e.g., drug discovery. A complex model might allow more reliable “extrapolations” towards the biological relevance of the effects observed in the real (patho-) physiological setting, e.g., a disease (Table 1).

Animal models are widely used in basic and applied biomedical research. Although complex, they still often meet the criteria of controlled manipulations of the parameters of interest. In this regard, the introduction of knockout and transgenic technologies allowed the