Cellular aging and the Proliferative Keratinocyte Homeostasis: Differentiation, Apoptosis and Senescence

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Abstract

To maintain a functional and healthy epidermis, the rate of proliferation must approximate the rate of degradation, i.e. homeostasis. In order to achieve an ample rate of proliferation, the epidermis is supplied with an unlimited capacity for cell renewal via the pool of proliferative keratinocytes. The achievement of an optimal rate of epidermal degradation is accomplished by the constant deletion of proliferative keratinocytes in the normal epidermis. The long time span for the life cycle of the proliferative keratinocyte in the epidermis and the proximity of the tissue to environmental insult lead to an increased potential for genetic aberration and mutagenesis. In order to decrease the potential for mutagenesis, the epidermis has developed three distinct methods to limit the life span of the pool of proliferative keratinocytes; terminal differentiation, apoptosis and senescence.

In the normal epidermis, terminal differentiation decreases the pool of proliferative keratinocytes, resulting in the formation of the stratum corneum with its barrier function. Apoptosis rapidly deletes genetically damaged proliferative keratinocytes. Disruption of either pathway can lead to numerous complications and disease states.

Senescence is the loss of the ability of a proliferative keratinocyte to undergo cell division. It is the least understood process employed in the skin to reduce the pool of these proliferative cells. The long life span of senescent cells in the epidermis is believed to contribute to the process of cellular aging due to cumulative damage. It has also been shown that chronological aging leads to an increase in the senescent cell population relative to that of proliferative keratinocytes. This results in a decrease in the rate of epidermal cell renewal.

Introduction

Arguably, homeostasis can be thought of as the fundamental tactical process that controls the maintenance of a regenerating tissue. In a physiological sense, homeostasis can be defined as the strategic balance between the rates of cell proliferation versus that of cell death in a multicellular organism. Simply, in order to maintain the size and function of the tissues of a living organism, for every cell that is created another cell must be deleted. An organism achieves this end via the dynamic equilibrium of regeneration and degradation [1, 2, 3].

The biological process of homeostasis is relevant to all regenerating tissues of an organism. But nowhere in the human body is the maintenance of this strategic balance between cell life and cell death more evident to the human eye than that of the skin. Human skin is both the first line of defense against environmental insults as well as the firstvisual impact to the eye. A disruption of he homeostasis of the skin can result in numerous problems relevent to the appearance of the skin. Disease states cause the severe disrution of homeostasis and greatly affect the skin's health and welfare [4].

Over decades of research, the mechanisms of proliferation are slowly being unraveled. But the paramount importance of the mechanisms of degeneration has just recently come to light. In this review, we describe the basic concept of homeostasis in the epidermis with a focus on the keratinocyte life cycle and the importance of cell death. Furthermore, we describe the current understanding of keratinocyte senescence and the process of cellular aging. Finally, we describe the consequences of disruptions in homeostasis and their relevance to the health of the skin.

Homeostasis and the Epidermis

Figure 1 depicts a simplified version of the life cycle of the keratinocyte. The original stem cell is stimulated by cell growth initiators (growth factors, cytokines) to undergo cell division. The result of this division is the development of a proliferative cell at the basal layer of the epidermis. The proliferative cell has the ability to react with both the internal and external environment such that, upon interaction with cell growth initiators, it can grow and divide. The purpose of the resulting new growth is to maintain a consistent size and function in a tissue that is continually deleting cells at the