METHOD FOR ENHANCING PROTECTIVE CELLULAR RESPONSES TO GENOTOXIC STRESS IN SKIN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of application Ser. No. 09/452,612, filed Dec. 1, 1999, now U.S. Pat. No. 6,337,065.

BACKGROUND

1. Field of the Invention

The invention is directed to methods and composition of using organic molecules termed pro-NAD agents capable of enhancing dermal and epidermal skin cell NAD content with a resulting enhancement of DNA repair and other protective responses to genotoxic stress in skin.

2. Description of the Background

The present application relates to methods and compositions capable of modulating and upregulating the cellular nicotinamide-adenine-dinucleotide (NAD) content by the topical application of chemical agents for the purpose of enhancing natural protective responses of skin cells to DNA damage. The methods and compositions are effective for the prevention and treatment of skin deterioration that results from DNA damage to cells of the skin. The symptoms of such skin deterioration are many and typically include the loss of moisture, fine lines, deep lines, wrinkles, and loss of elasticity as well as atrophic sclerosis and other blemishes of skin. Skin deteriorates with age as a natural consequence of prolonged exposure to internal and external factors. Internal deterioration factors include natural metabolic byproducts such as free radicals which cause the aging of all tissues. External deterioration factors include ionizing radiation such as sunlight and chemical insults such as pollution and cigarette smoke. In theory, skin care methods and compositions should inhibit, or slow the process of skin deterioration by counteracting these internal and external factors. Unfortunately, current methods and compositions for skin care are generally reactive rather than proactive. That is, current methods and compositions reduce or obscure the signs of aging but have minimal or no effect on the underlying progressive and cumulative biochemical processes that cause skin deterioration. It is therefore desirable to have a skin care method and composition which not only reduce the symptoms of deterioration but also treat the underlying causes of skin deterioration in such a way that deterioration can actually be retarded. To understand the limitations of current methods and compositions, it is necessary to understand the function and stricture of the skin and the mechanisms of skin deterioration.

At ten pounds, the skin is the largest organ in the body. FIG. **1** shows a diagram of skin marking the location of the two major cell types present in skin, namely fibroblasts located in the dermal layer of the skin and keratinocytes located in the epidermal layer of the skin. The skin provides the first line of defense between the body's interior and harmful environmental insults by well established physical and biochemical mechanisms. Physical protection mechanisms include the relatively impermeable barrier the skin provides. The skin can, to some extent, repel and absorb insults such as chemicals and ultraviolet light so that while the skin may be damaged, the underlying tissue is preserved. Biochemical mechanisms include the innate and acquired immune systems. Microbiological pathogens are repelled by immune responses at the epidermal level involving Langerhans cells, keratinocytes, cytokines, polynuclear cells, endothelial cells, mast cells, and lymphocytes.

Structurally, the skin comprises epithelial tissue (the epidermis) in the outer layer and beneath it, connective tissue (the dermis), and beneath that, the fatty tissue (hypodermis). The epidermis is not vascularized and regenerates every four to six weeks. Its primary function is to maintain the body's skin integrity, acting as a physical barrier to toxic agents, dirt, bacteria, microorganisms, and physical insults. The dermis is beneath the epidermis and functions by providing strength, support, blood, and oxygen to the skin. The principal cell components of the dermis are fibroblasts although it also contains sweat glands, sebaceous glands, hair follicles, and small fat cells. Hypodermis, also known as the superficial fascia, attaches the dermis to the underlaying strictures. Its function is to promote an ongoing blood supply to the dermis for regeneration.

The mechanisms of skin deterioration involve a gradual and progressive process that begins from birth. Internal factors that contribute to skin aging include toxic metabolic byproducts, autoimmune diseases, and genetic predisposition. The consequences of internal deterioration can be observed over the entire body from the skin to the internal organs. While the mechanisms of internal deterioration are not completely understood, somatic mutation has been shown to be a contributing factor. Under the somatic mutation theory, cells gradually lose their youthful characteristics and their capacity to divide by the accumulation of mutations (errors) in their genetic code. These mutations may be caused by free radicals or alkylating agents generated in metabolism that lead to unrepaired DNA damage. Over time, mutations accumulate in the body until the cell can no longer divide or produce functional proteins.

External factors such as chemical and physical agents in the environment can also cause DNA damage that leads to skin deterioration. The external factors include sunlight, pollution, and ingested chemicals from smoking or from food.

Deterioration of skin leads to changes in dermal thickness and elasticity due to increased crosslinking of collagen. Epidermal regeneration increases in activity while metabolism, sweat glands, and vascularization, all decrease in activity. The damage from internal and external factors is progressive and cumulative and results in the appearance of deterioration associated with aged skin.

Related to the somatic mutation theory, both internal and external factors contribute to oxidative stress, which in turn results in DNA damage. In humans, oxidative stress and DNA damage is caused by factors such as hyperbaric oxygen, gamma radiation, ultraviolet radiation, ozone, peroxides, free radicals, alkylating agents, and redox cycling drugs. While total oxidative stress and DNA damage may be reduced by living in a low pollution environment and avoiding sunlight, they cannot be eliminated. Some factors like ionizing radiation are present in all environments at a low level and other factors are byproducts of metabolism and cannot be totally eliminated. Further, urban environments have high levels of ground level pollution from a variety of sources that are not likely to be reduced in the near future. However, while DNA damage cannot be avoided, not all DNA damage leads to mutations.

DNA damage does not necessarily lead to mutation because a normal cell contains diverse and effective systems for repairing damaged DNA. There are at least 50, and possibly more than 100 genes involved in DNA repair. The importance of good DNA repair in retarding skin deterioration is most noticeable in patients that suffer from DNA repair defects such as xeroderma pigmentosum (XP). XP