

Regulation of cell function by citric acid: Roles in beauty care, skin whitening and anti-aging

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Citric acid is a substance produced naturally in citrus fruits, such as grapefruits, oranges and lemons, and makes an addition of sour taste to foods and drinks. Citrate synthase (CS) produces citric acid and initiates citric acid cycle (also known as tricarboxylic acid cycle [TCA] and the Krebs cycle) that assumes respiratory activity in mitochondria of all types of cells. In general, chemical properties of CS are beneficial for skin care and often contained in skin care products; however, its cosmetic effect is still unproven scientifically. To address this issue, we studied a physiological role of citric acid by producing mice lacking a gene encoding extra-mitochondrial citrate synthase (hereafter, eCS). eCS proteins are expressed in several types of cells such as neurons, sperm and hair sheath cells in mice. The eCS proteins are also produced in human cells; nonetheless, its biological role is unclear. From general knowledge about citric acid, we assumed that eCS deficiency might reduce cellular activity, presumably causing metabolic problems. Expectedly, *eCs*-deficient mice exhibited hypopigmented hairs due to the reduction of cellular activity of melanocyte stem cells, regardless of male or female. Furthermore, the frequency of mating behavior of the male mice was low, and their sperm-fertilizing ability decreased age-dependently, resulting in male subfertility. Moreover, graying hairs went age-dependently forward to white hairs in addition to hair loss. Interestingly, the supplementation of cyclic AMP (cAMP) improved lower cellular activities in sperm and melanocytes isolated from *eCs*-deficient mice under the in vitro condition, although the supplementation of citric acid was unaffected. We discovered the role of eCS in pigmentation and reproduction. We further propose that enhancement of eCS activity (or local application of cAMP) not only suppresses hair graying, but also improve male sexual dysfunction.