Study of the Role of Eicosanoids in Melanocyte-stimulation in Post-inflammation Pigmentation

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Skin pigmentation after inflammation is a well recognized phenomenon, but its mechanisms have been unknown yet. A number of substances are considered to contribute to post-inflammatory pigmentation, and eicosanoids are one of the most important mediators. Eicosanoids, prostaglandins (PGs) or leukotrienes (LTs), show potent pharmacological activity in various tissues, and actively synthesized and degraded in the skin, and contribute to the pathogenesis of a number of skin diseases such as UV-dermatitis, atopic dermatitis, urticaria and psoriasis. We examined the synthesis of leukotrienes in human melanoma cells in order to assess the function of leukotrienes in human melanocytes. The enzyme activity of LTA₄ hydrolase, which catalyzes the conversion of LTA₄ to LTB₄, was detected in the supernatant of cultured human melanoma cells (MeWo cells) and melanoma cells obtained from patients. Immunoblotting analysis using an anti-human LTA₄ hydrolase antibody demonstrated LTA₄ hydrolase as a 70-kDa protein in both MeWo and melanoma cells. Considerable enzyme activity of LTC₄ synthase, which catalyzes the conversion of LTA₄ to LTC₄, was detected in the microsomal fraction of both MeWo and melanoma cells. The HPLC profile of the LTC₄ synthase reaction products revealed that LTC₄ was the main product. LTD₄ was not detected under these conditions, indicating that the microsomal fraction of human melanoma cells lacks the membranebound γ-glutamyl transferase that converts LTC₄ to LTD₄. LTC₄ synthase activity was inhibited by the addition of MK-886, and was not altered by treatment with N-ethylmaleimide (NEM) or 1-chloro-2,4-dinitrobenzene (CDNB). These results indicate that the enzyme responsible for the conversion of LTA₄ to LTC₄ in human melanoma cells is LTC₄ synthase rather than a nonspecific or microsomal glutathione-s-transferase. These results also suggest that human melanoma cells can generate LTB₄ and LTC₄ from LTA₄, and that this process is catalyzed by two enzymes: LTA₄ hydrolase and LTC₄ synthase.