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Review article

The application of skin metabolomics in the context of transdermal drug delivery

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ABSTRACT

Metabolomics is a powerful emerging tool for the identification of biomarkers and the exploration of metabolic pathways in a high-throughput manner. As an administration site for percutaneous absorption, the skin has a variety of metabolic enzymes, except other than hepar. However, technologies to fully detect dermal metabolites remain lacking. Skin metabolomics studies have mainly focused on the regulation of dermal metabolites by drugs or on the metabolism of drugs themselves. Skin metabolomics techniques include collection and preparation of skin samples, data collection, data processing and analysis. Furthermore, studying dermal metabolic effects *via* metabolomics can provide novel explanations for the pathogenesis of some dermatoses and unique insights for designing targeted prodrugs, promoting drug absorption and controlling drug concentration. This paper reviews current progress in the field of skin metabolomics, with a specific focus on dermal drug delivery systems and dermatosis.

Contents

Introduction

Metabonomics/metabolomics is a research field that is concerned with methods for analyzing the types of, quantities of and variations among the small-molecule metabolites that are produced from endogenous or exogenous substances by cells, tissues or organisms under physiological conditions or when influenced by pathological stimuli [1]. Metabolomics is

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characterized by a combination of large-scale omics experiments and chemometrics methods, which are conducted using technology that is high-throughput and has high resolution and sensitivity. Metabolomics combines modern spectroscopic detection technology, pattern-recognition technology and relevant databases [1] to identify biomarkers and metabolic regulatory networks so as to clarify the pathogenesis of an organism, reveal the pharmacology and toxicology of drugs, explore targets for disease prevention and discover new drugs.

Representing the body's first barrier to exogenous substances, the skin transfers topical signals internally through active metabolic pathways to influence physiological activities and regulate body homeostasis, thereby permitting adaptation to a variety of external environments. The skin is a metabolically active organ, as most of the enzymes that are expressed in the liver are also expressed in the skin [2,3]. A two-phase reaction occurs in skin metabolism. Specifically, phase I metabolism comprises oxidation, reduction and hydrolysis, while phase II metabolism is a conjugation reaction. The skin is rich in enzymes involved in these reactions; such enzymes include cytochrome P450, the flavin monooxygenase family of enzymes, nonspecific esterase and conjugating enzymes (transferases) [4,5]. As the main phase I metabolic enzyme, cytochrome P450 is involved in the metabolism of many endogenous substances, such as steroids, fatty acids, prostaglandins (PG), glucocorticoids and leukotrienes (LT), in addition to several exogenous substances, such as drugs and metabolic poisons [4,5]. Enzymatic activity increases progressively from the skin surface to deep sites and is approximately 1%–10% that of the liver [6]. A recent survey showed that in human skin, the activity of phase II metabolic enzymes is higher than that of the corresponding phase I enzymes [7]. Transdermal delivery is a typical method that is used in external medicine. During this process, a drug is absorbed, metabolized and excreted by the skin. These steps are significant in transdermal delivery systems, as the first-pass effect of skin on a drug is weaker than that of the liver. Owing to the unique anatomical sites and structure of skin and to its relative impermeability to most drugs, few studies on skin metabolism have been conducted, resulting in slow progress in the transdermal delivery field [6]. However, adverse biological effects of abnormal skin, including oxidative stress and hyperplasia, can be repaired and regulated by adjusting the levels of metabolites, known as metabolomics biomarkers [74]. Metabolomics, a novel area of research, has mainly been focused on analyzing organs and such body fluids as blood and urine. However, using skin biopsies to examine intracellular metabolites by metabolomics analysis may yield direct signatures of cellular processes at the local target tissue site [8], especially for dermatosis. Consequently, skin metabolomics can be used to investigate metabolic pathways and identify variations in relevant metabolites, so as to elucidate the mechanism by which the skin responds to stimuli.

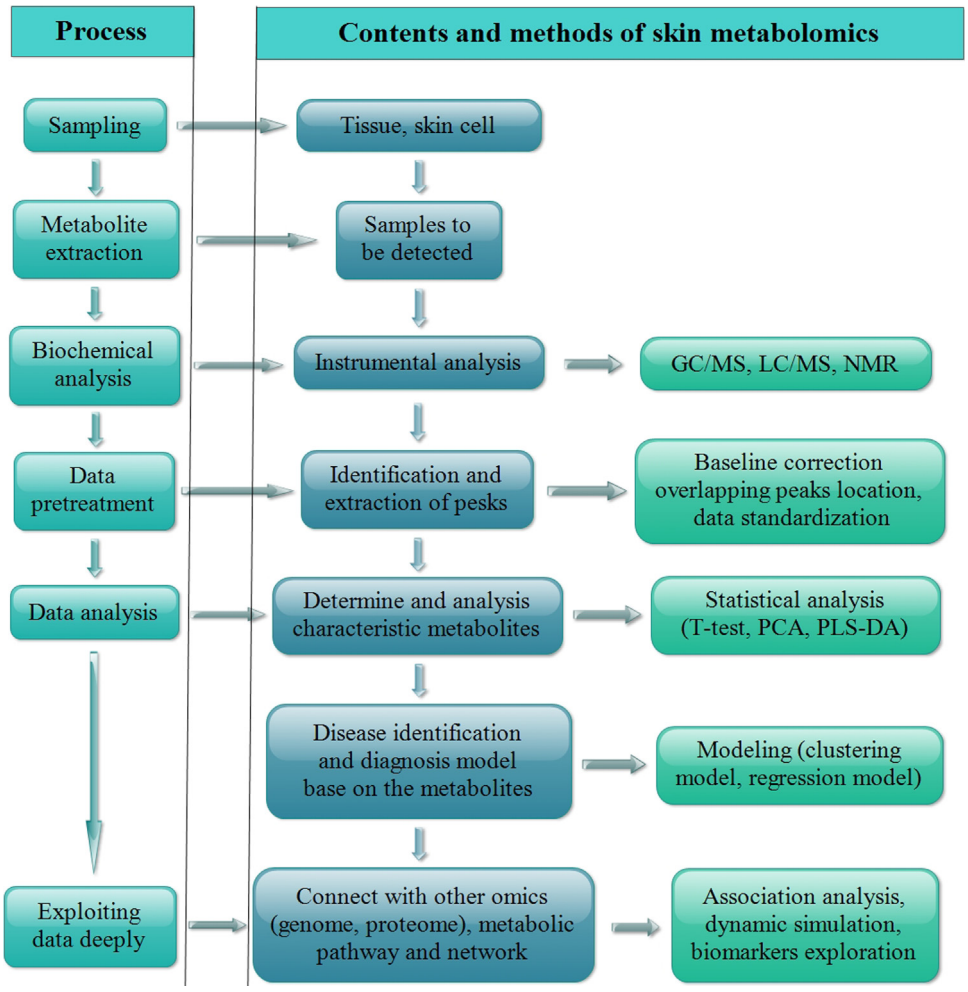

Fig. 1. The complete process of dermal metabolomics.