



Drug metabolism and Genotoxicity in Different Skin Model System

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DESCRIPTION

Drug metabolism and genotoxicity in different skin model systems are critical aspects of dermatological research, pharmacology, and toxicology. The skin, being the largest organ of the human body, serves as a primary barrier against environmental insults and plays a significant role in drug absorption and metabolism. Understanding how drugs interact with skin cells and tissues, and assessing their potential to cause genetic damage (genotoxicity), is essential for developing safe and effective dermatological treatments. Various skin model systems, ranging from *in vitro* cell cultures to complex *in vivo* models, are employed to study these phenomena.

Drug metabolism in the skin involves the enzymatic transformation of pharmaceutical compounds. The skin expresses a range of metabolizing enzymes, including Cytochrome P450s (CYPs), esterases, and transferases. These enzymes can modify drugs through oxidation, reduction, hydrolysis, and conjugation reactions. The resulting metabolites may have different pharmacological or toxicological properties compared to the parent compound. Studying drug metabolism in skin models helps predict systemic exposure following topical application and potential local and systemic adverse effects.

Primary human keratinocytes and dermal fibroblasts are commonly used *in vitro* models for studying skin metabolism. Keratinocytes, the predominant cell type in the epidermis, express various CYP enzymes, particularly CYP1A1, CYP2E1, and CYP3A4. These enzymes participate in the metabolism of many drugs and xenobiotics. Dermal fibroblasts, located in the dermis, also contribute to drug metabolism through their enzymatic activity. By using these primary cells, researchers can investigate the metabolic fate of drugs in the skin and identify specific enzymes involved in their transformation.

Another valuable *in vitro* model is the Reconstructed Human Epidermis (RHE). RHE consists of cultured human keratinocytes that differentiate and stratify to form a multilayered structure resembling the human epidermis. This model provides a more physiologically relevant system compared

to monolayer cultures, as it maintains the architecture and barrier function of the epidermis. RHE models are used to evaluate the metabolism of topically applied drugs, assess their penetration through the skin, and investigate potential irritancy or toxicity.

Organotypic skin models, which include both epidermal and dermal components, offer even greater complexity. These models are generated by culturing keratinocytes on a dermal equivalent composed of fibroblasts embedded in a collagen matrix. Organotypic models the three-dimensional structure of human skin and support the interactions between epidermal and dermal cells. They are valuable for studying drug metabolism, as they provide a more comprehensive representation of skin physiology and enzymatic activity.

In addition to *in vitro* models, *ex vivo* human skin is frequently used in drug metabolism studies. This approach involves using skin biopsies obtained from human donors or surgical procedures. *Ex vivo* human skin maintains the native architecture and enzyme expression patterns, making it an excellent model for studying drug penetration, metabolism, and potential adverse effects. It allows for the assessment of drug distribution within different skin layers and the identification of metabolites formed *in situ*.

Animal models, particularly rodents, are also employed to investigate drug metabolism in the skin. Mice and rats have been extensively used due to their availability, ease of handling, and genetic similarity to humans. However, there are notable differences between rodent and human skin, such as thickness, hair density, and enzyme expression levels. These differences must be considered when extrapolating results from animal studies to humans. Despite these limitations, animal models provide valuable insights into the *in vivo* metabolism of drugs and their systemic effects following topical application.

Genotoxicity refers to the ability of a substance to cause damage to the genetic material within a cell. Assessing genotoxicity is crucial for evaluating the safety of dermatological products, as genetic damage can lead to mutations, cancer, and other adverse

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health effects. Various assays are used to assess genotoxicity in skin model systems, including the Ames test, micronucleus assay, and comet assay.

The Ames test, also known as the bacterial reverse mutation assay, is a widely used *in vitro* assay to screen for genotoxic potential. It uses specific strains of the bacterium *Salmonella typhimurium* that carry mutations making them unable to synthesize histidine. When exposed to a genotoxic compound, mutations can occur, allowing the bacteria to regain the ability to grow in a histidine-free medium. Although the Ames test does not directly involve skin cells, it serves as an initial screening tool for potential genotoxicity.

The micronucleus assay is another widely used method for assessing genotoxicity. It detects the formation of micronuclei, which are small, extranuclear bodies containing chromosomal fragments or whole chromosomes that were not incorporated into the daughter nuclei during cell division. The assay can be performed using cultured skin cells, such as keratinocytes or fibroblasts, to evaluate the genotoxic effects of drugs or their metabolites.

The comet assay, also known as the single-cell gel electrophoresis assay, is a sensitive technique for detecting DNA strand breaks

in individual cells. Skin cells exposed to a genotoxic agent are embedded in agarose on a microscope slide, lysed to remove membranes, and subjected to electrophoresis. DNA fragments migrate towards the anode, forming a "comet tail" whose length and intensity reflect the extent of DNA damage. The comet assay can be used with various skin cell types to assess genotoxicity at the cellular level.

CONCLUSION

In conclusion, understanding drug metabolism and genotoxicity in different skin model systems is fundamental for the development of safe and effective dermatological therapies. Various *in vitro*, *ex vivo*, and *in vivo* models provide complementary insights into how drugs are metabolized in the skin and their potential to cause genetic damage. Each model has its strengths and limitations, and often a combination of models is used to obtain a comprehensive assessment. Advances in skin model systems continue to improve our ability to predict human responses to drugs, ultimately contributing to better patient outcomes and reduced risk of adverse effects.