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Perspective

Quantitative Assessment of Hydrolases Involved in Human Drug Metabolism

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DESCRIPTION

Protein abundance patterns of drug-metabolizing hydrolases in human tissues are a central topic in pharmacology because these enzymes influence how medicines, environmental chemicals, and endogenous compounds are transformed and cleared from the body. Hydrolases, such as carboxylesterases, epoxide hydrolases, and certain peptidases, perform reactions that break chemical bonds through the addition of water. In the liver and intestine, these enzymes contribute to both detoxification and activation of therapeutic agents. Understanding how much of each hydrolase is present in these tissues is important for predicting drug response, interindividual variability, and potential adverse reactions.

Targeted proteomics addresses many of these challenges by focusing on a predefined set of proteins or peptides. In this approach, specific peptides that uniquely represent a hydrolase of interest are selected in advance. These peptides are monitored by the mass spectrometer using techniques such as Selected Reaction Monitoring (SRM) or Parallel Reaction Monitoring (PRM). Often, stable isotope-labeled versions of the selected peptides are added as internal standards. Because the instrument is programmed to detect only these peptides, sensitivity and reproducibility are greatly improved. This method allows accurate, absolute or relative quantification of hydrolases even at low levels.

When comparing targeted and global approaches in the context of human liver and intestine, several differences become apparent. Global proteomics provides a comprehensive view. It allows researchers to observe not only hydrolases but also enzymes from other metabolic pathways, transporters, structural proteins, and signaling molecules. This broad perspective is valuable for understanding the overall biochemical environment of the tissue and for discovering unexpected changes associated with disease, drug exposure, or genetic variation. For example, a global study might reveal that under certain pathological conditions, hydrolase expression is altered alongside changes in inflammatory proteins or oxidative stress markers. Such findings can generate hypotheses for further investigation.

Sample preparation also plays a role in comparative outcomes. Liver and intestine have distinct structural and biochemical characteristics. The liver is rich in blood and contains a dense cellular architecture, whereas the intestine includes multiple layers, including epithelium, connective tissue, and muscle. Isolating enterocytes from the intestinal mucosa requires careful handling to avoid contamination with other cell types. Inconsistent preparation can influence proteomic measurements in both global and targeted experiments. Standardized protocols for tissue collection, storage, protein extraction, and digestion are essential for reliable comparison.

From a practical standpoint, the choice between targeted and global proteomics depends on the research question. If the aim is to gain an overview of metabolic capacity in a given tissue or to discover unknown changes in disease, global proteomics is advantageous. It allows the survey of a broad range of proteins without predefined assumptions. If the goal is to quantify specific hydrolases with high accuracy for predictive modeling or clinical correlation, targeted proteomics is more appropriate. Many modern studies integrate both approaches. A global analysis may be conducted first to identify relevant enzymes and patterns, followed by targeted quantification to confirm and refine the findings.

The clinical implications of these comparative studies are significant. Knowledge of hydrolase abundance in liver and intestine informs drug design by identifying potential metabolic hot spots. Pharmaceutical scientists can modify chemical structures to avoid rapid hydrolysis or, in the case of prodrugs, to ensure efficient activation. Clinicians can better understand why certain patients respond differently to the same medication. In personalized medicine, enzyme abundance data may one day complement genetic testing to guide dose selection and drug choice.

Advances in mass spectrometry, data analysis software, and sample processing continue to improve both global and targeted proteomics. New acquisition methods increase depth and consistency in global studies, while multiplexed targeted assays allow the simultaneous measurement of dozens or even

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hundreds of proteins in a single run. As these technologies mature, the distinction between the two approaches may become less rigid, with hybrid methods combining wide coverage and high precision.

In conclusion, the comparative analysis of protein abundance for clinically relevant drug-metabolizing hydrolases in human liver and intestine illustrates the strengths and limitations of both targeted and global proteomics. Global methods offer breadth, context, and discovery potential, revealing broad patterns of enzyme distribution across tissues. Targeted methods deliver depth, precision, and reproducibility, enabling accurate quantification of specific enzymes that drive drug metabolism. Together, these approaches provide a comprehensive understanding of how hydrolases contribute to drug disposition, interindividual variability, and therapeutic outcomes. This integrated knowledge base supports safer and more effective use of medicines and contributes to the ongoing improvement of pharmacological science.