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Database issue

VARIDT 4.0: distribution variability of drug transporters

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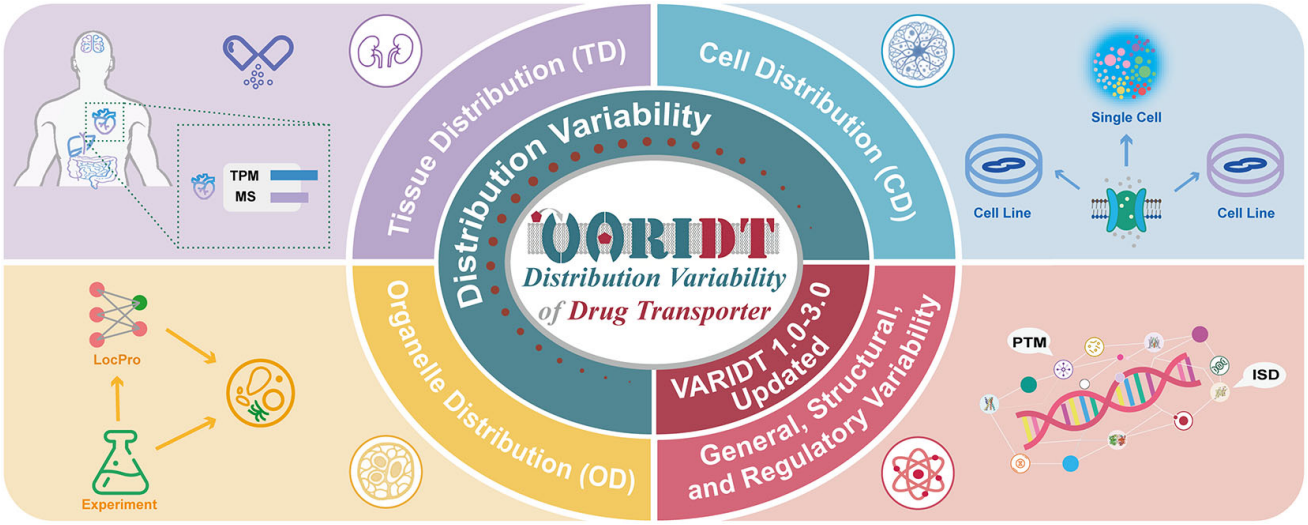
Abstract

The multilevel distribution variability of drug transporters—from tissues to cells and organelles—is critical for understanding drug response, drug–drug interactions, and multidrug resistance. The absorption, dispersion, metabolism, and excretion properties of drugs are codetermined by these multilevel distribution patterns, including tissue-specific expression, cellular heterogeneity, and subcellular localization. However, a public database that systematically integrates these crucial data of drug transporter distribution variability has been lacking. Therefore, in this major update, VARIDT 4.0 was developed to provide a comprehensive resource, incorporating 25 797 tissue-level expression profiles, 451 830 cell-level expression records, and 1034 subcellular localization entries. Additionally, the foundational modules on general, structural, and regulatory variability were extensively updated. This multilevel variability data is highly relevant to the transport of 889 approved and 221 clinical trial drugs, as well as 689 endogenous metabolites, implicated in the treatment of 558 diseases. Furthermore, by integrating these new distribution layers with its existing data, VARIDT 4.0 now enables comprehensive consideration of how a transporter's function is modulated by its specific spatiotemporal context. Overall, VARIDT 4.0 is expected to be a valuable data repository for system pharmacology, serving as an essential complement to existing pharmaceutical databases, and is freely accessible without login at https://idrblab.org/varidt/.

Graphical abstract



Introduction

Drug transporters (DTs) are a variety of molecules essential for drug absorption, dispersion, metabolism, and elimination [1–3], and the variability of DTs is crucial due to their ability to affect drug efficacy and safety [4–6]. VARIDT database was therefore developed to describe variability information for hundreds of DTs from multiple directions: general variability [7], structural variability [8], regulatory variability [9], etc.

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Recently, the distribution variability of DTs among different biological levels (from tissue level, then to cell level, and finally to organelle level) was found critical for the assessment of therapeutic efficacy [10], estimation of adverse effects [11], reversal of drug resistance [12], and design of new drug [13]. Particularly, at the tissue level, DTs' differential expression in various tissues is responsible for the varied efficiency of drug dispersion in different parts of human body [14], the understanding of which is therefore valuable for revealing tissue-specific drug response and side effect [15]; at the cell level, DTs' distribution variability is closely relevant to the frequent occurrence of drug resistance and the varied outcomes of clinical prognosis [16], the leveraging of which can facilitate the perception of disease-specific dispersion and excretion of drug [17]; at the organelle level, variances in DTs' subcellular localization are closely linked to abnormal cell growth and disease progression [18], the knowledge of which can inspire novel strategy for designing drug of improved efficacy and restricted toxicity by targeting the specific subcellular compartment [19]. Due to the importance and complexity of DT-driven absorption, dispersion, metabolism, and excretion (ADME) of drugs, the distribution variability of DTs has been considered as an essential piece of the puzzle in related fields, and it is therefore highly demanded to have these recently accumulated critical data for enriching the landscape of drugs' efficacy and safety [20–22].

Existing DT-related databases have made great contributions by offering a range of key data that helps in understanding the distribution, function, and structure of DTs. For instance, TransporterDB gives detailed classification of transporters, physiological roles, and expression profiles across various tissues, enabling researchers to explore transporter-specific distributions and their influence on drug pharmacokinetics [23]. Additionally, specialized databases, such as Transporter Classification Database (TCDB), provide in-depth functional and structural information on various transporters, including their evolutionary relationships, which are key for designing drug of better targeting profiles [21]. ISTransbase focuses on the in-depth analysis of transporter substrate and inhibitor specificity, offering valuable data on the functional roles of transporters in drug ADME, with particular attention to human-specific transporters and their relevance in clinical pharmacology [24]. However, the critical data of DTs' distribution variability discussed above are not sufficiently covered by existing knowledge bases (including the previous versions of our VARIDT).

Herein, VARIDT was thus updated by collecting all three levels of distribution variability data for all the DTs in our database. Particularly, at the tissue level, a total of 19 658 transcriptomics and 6139 proteomics profiles of 404 DTs differentially expressed in 52 tissues (containing the vast majority of metabolic organs or biological barriers) were accumulated; at the cell level, the variability data of 402 DTs among 1278 cell lines from human and 9 model organisms (including rat, mouse, hamster, rabbit, bovine, monkey, horse, chicken, and pig) covering 121 disease classes (lung cancer, hepatocellular carcinoma, etc.) were accumulated; at the organelle level, a total of 1034 subcellular localization data associated with 68 organelles (containing all major functional organelles of eukaryotic cells) were provided for a total of 422 DTs. As a result, the distribution variability data of 425 DTs were integrated into VARIDT 4.0 and found to be closely related to the transportation of 889 approved drugs, 221 clinical trial drugs, and 689 endogenous metabolites, involving widely in treating 558 diseases. Furthermore, a comprehensive update of three core modules of VARITD: general, structural, and regulatory variabilities, was conducted. By systematically integrating distribution data of DTs across three levels and extensively updating previously collected variability data of DTs on general, structural, and regulatory variability, VARITD provides essential data resources for analyzing drug ADME properties, designing targeted drug delivery systems, and evaluating drug safety profiles. It is now freely accessible at https://idrblab.org/varidt/.

Factual content and data retrieval

To address the critical role of DT distribution variability in drug discovery and therapeutics, the VARIDT database has been substantially expanded to version 4.0. The central feature of this release is the introduction of three hierarchical levels of data previously uncatalogued: tissue-level, cell-level, and organelle-level variability. This new information has been organized and presented as three corresponding and distinct new data submodules. Alongside these additions, the preexisting modules for general variability (v1.0), structural variability (v2.0), and regulatory variability (v3.0) have been extensively updated and enriched with the latest findings. The overall architecture of the expanded database is shown in Fig. 1, and the contents of the new submodules, along with the key enhancements to the established ones, are elaborated below.

Tissue-level distribution variability of DTs

Tissue-specific distribution of DTs represents a critical determinant of pharmacokinetics and therapeutic outcomes [25, 26]. These transporters exhibit highly heterogeneous expression patterns across pharmacologically relevant organs, including liver, kidney, intestine, and blood–brain barrier [4]. Such tissue-specific expression profiles fundamentally regulate drug ADME processes, thereby influencing drug efficacy and safety. Systematic documentation of transporter tissue distribution data is essential for multiple applications: predicting tissue-specific drug–drug interactions [25], assessing organ-specific toxicity risks [4], optimizing drug delivery strategies [27], and developing physiologically based pharmacokinetic (PBPK) models [28]. In other words, integration of transporter expression profiles with drug substrate information provides a valuable framework for elucidating interindividual variability in drug response and advancing precision medicine.

Therefore, VARIDT systematically integrated tissue distribution data of DTs through a structured workflow. Literature searches were performed using keyword combinations including "human tissue + transcriptome" and "human tissue + proteome" to identify tissue-level transcriptomic [29] and proteomic [30] datasets. Expression data for DTs were subsequently extracted from these primary resources. This curation process yielded 25 797 tissue distribution records, comprising 19 658 transcriptomic entries for 404 transporters across 52 tissue types, and 6139 proteomic entries for 250 transporters across 32 tissues. As illustrated in Fig. 2, VARIDT integrates two molecular-level tissue-specific expression visualizations, which are crucial for elucidating drug disposition and provide a more robust basis for predicting organ-specific efficacy and toxicity. The expression profiles of each DT at both the tran-

Figure 1. The multilevel distribution and foundational variability data of DTs provided in VARIDT 4.0. (**A**) The tissue-level distribution of DTs; (**B**) the cellular-level distribution of DTs; (**C**) the organelle-level distribution of DTs; and (**D**) the comprehensive updates to foundational variability data (general, structural, and regulatory).

scriptomic and proteomic levels are mapped onto an interactive human organ atlas encompassing over 20 healthy tissues (Fig. 2A). To enable direct comparative analysis, side-by-side plots display messenger RNA and protein abundance for each tissue where both datasets are available (Fig. 2B).

Cell-level distribution variability of DTs

Cell-type-specific expression of DTs represents a critical determinant of drug selectivity [31]. Single-cell transcriptomic studies have revealed significant variations in transporter expression profiles across different cell types within the same tissue [32]. In the liver, for instance, hepatocytes, Kupffer cells, stellate cells, and endothelial cells each express distinct transporter repertoires, directly influencing cell-specific drug distribution and effects [33]. Expression heterogeneity is also observed within individual cell types: differential transporter expression among cancer cell subpopulations in the tumor microenvironment contributes to heterogeneous chemotherapy sensitivity, constituting a key mechanism of drug resistance [34]. Disease states and drug-induced modulation further alter transporter expression in specific cell populations, affecting therapeutic outcomes [35]. Therefore, establishing comprehensive databases integrating cell-type-specific transporter expression data from cell lines and single-cell sequencing is essential for understanding drug selectivity and predicting therapeutic response heterogeneity.

Cell-level distribution data of DTs were systematically incorporated into VARIDT through a comprehensive curation strategy. Literature searches were conducted using keyword combinations including "single cell + transcriptome," "single cell + proteome," "cell line + transcriptome," and "cell line + proteome" to identify relevant datasets, including single-cell transcriptomic [36], cell line transcriptomic [37], and cell line proteomic [38] resources. Expression data for DTs were subsequently extracted from these primary datasets. This curation yielded 451 830 cell-level records, encompassing 51 644 single-cell transcriptomic entries for 401 transporters across 180 cell types, 340 777 cell line transcriptomic entries for 402 transporters across 1201 cell lines, and 59 409 cell line proteomic entries for 111 transporters across 949 cell lines. The cell-level variability data for DTs were shown in Fig. 3, which integrated data from both single-cell sequencing and cell line profiling across over a thousand distinct cell types. For single-cell data (Fig. 3A), a composite visualization is employed: a sunburst chart displays the hierarchical classification and proportion of expressing cells within major lineages (e.g. immune cells, epithelial cells), which is complemented by a scatter plot detailing expression in specific subtypes. Conversely, Fig. 3B depicts the expression across numerous cell

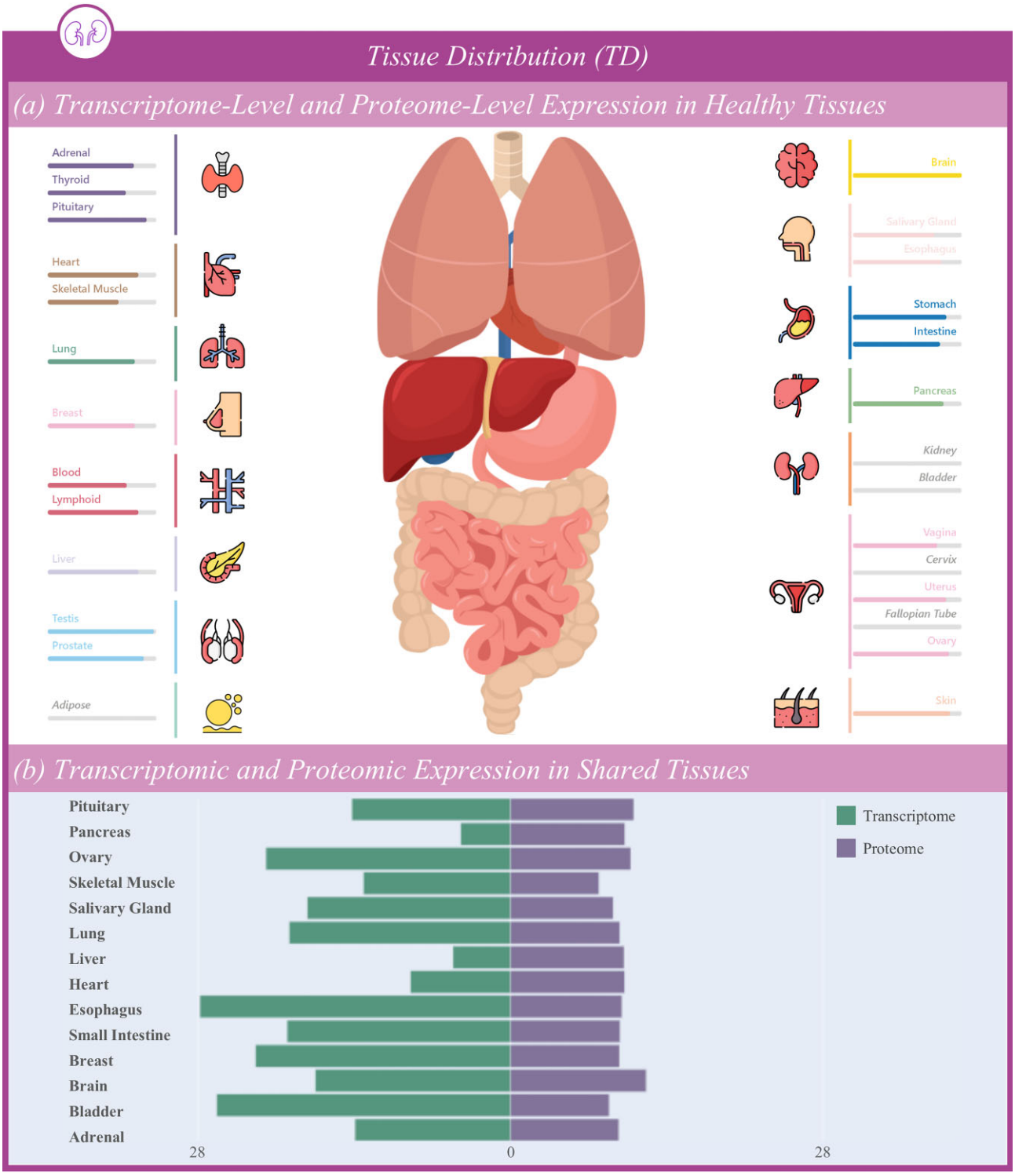

Figure 2. Expression profiles of DTs across human tissues at transcriptomic and proteomic levels. (**A**) Cross-tissue expression patterns of DTs showing transcriptomic and proteomic abundance. (**B**) Correlation between transcriptomic and proteomic abundance of DTs within individual tissues.

lines, featuring an interactive bar chart of mean transcriptomic and proteomic levels. Users can dynamically group the cell lines by disease category (e.g. Astrocytoma, Brain Cancer) via a dropdown menu. This dual-view interface provides a powerful resource for identifying precise cellular drug targets, assessing expression heterogeneity in disease, and selecting appropriate experimental models.

Organelle-level distribution variability of DTs

Subcellular localization and expression variation of DTs represent critical determinants for elucidating drug action mechanisms and toxicological effects [39, 40]. Transporters are distributed not only in plasma membranes but also across various organellar membrane systems [41]. The SLC25 family transporters in mitochondrial inner membranes regulate drug up-

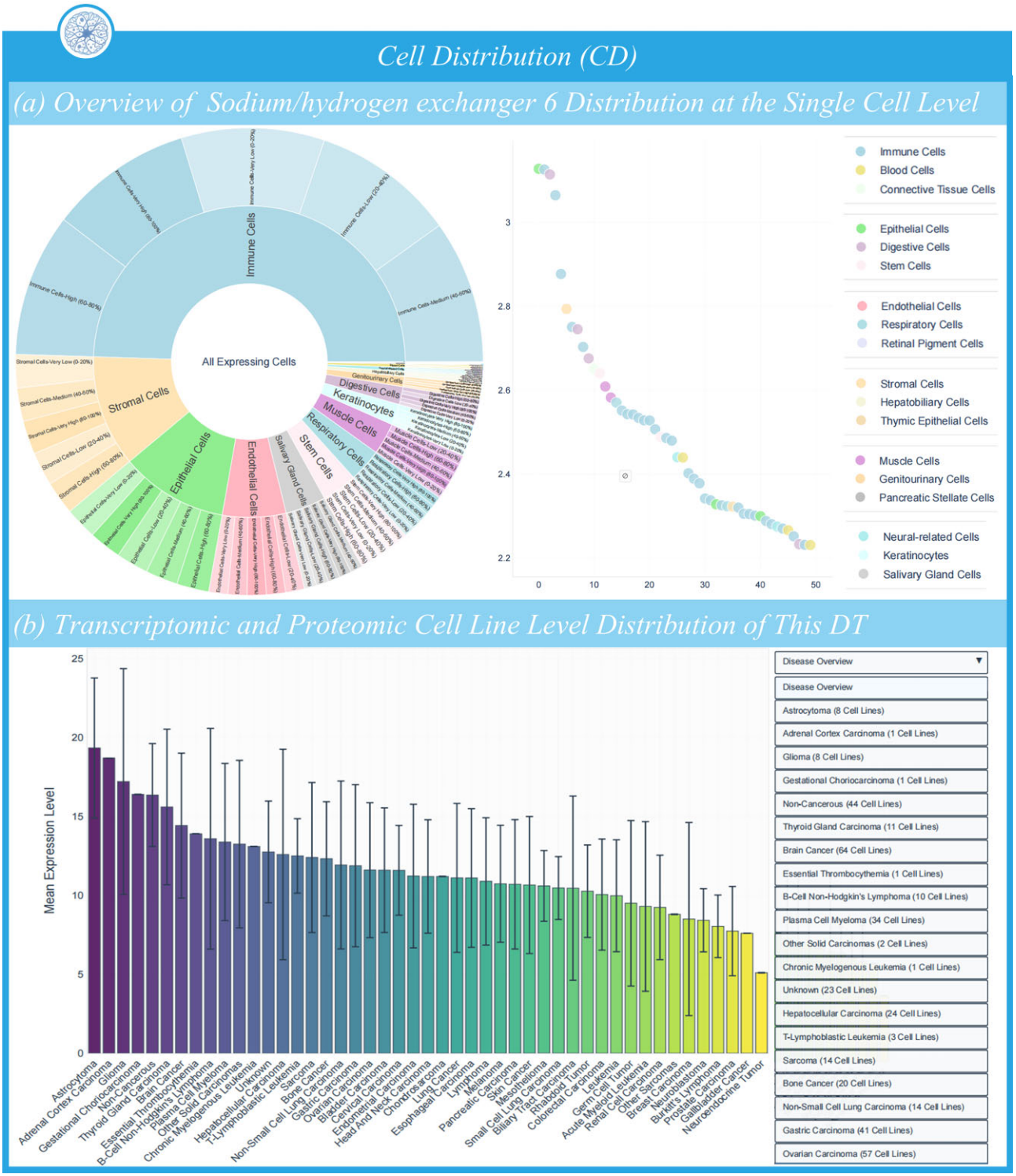

Figure 3. Cellular heterogeneity of DT expression across human cell types and cell lines. (**A**) Single-cell transcriptomic expression profile of sodium/hydrogen exchanger 6 (NHE6) across diverse human cell types. (**B**) Transcriptomic and proteomic abundance of NHE6 in a panel of disease-derived cell lines.

take into mitochondria, determining the efficacy and toxicity of mitochondria-targeted therapeutics [19]. Lysosomal membrane transporters such as SLC46A3 control drug accumulation in lysosomes, which is particularly crucial for the intracellular distribution of weakly basic drugs [42, 43]. Transporters in the endoplasmic reticulum and Golgi apparatus participate in metabolite trafficking, affecting biotransformation efficiency [44]. Nuclear envelope transporters modulate nucleocytoplasmic shuttling of drugs targeting nuclear components [45, 46]. Under pathological conditions, organellar transporter expression and localization undergo alterations: upregulation of lysosomal transporters in tumor cells leads to chemotherapeutic drug sequestration in lysosomes, reducing drug efficacy [47, 48]. In other words, systematic collection of transporter subcellular localization data and their dynamic changes under various physiological and pathological conditions is essential for understanding mechanisms of drug efficacy and toxicity, and inspire novel strategy for designing drug of improved efficacy and restricted toxicity by targeting the specific subcellular compartment [4].

Therefore, VARIDT systematically collected the subcellular localization data of DTs through a comprehensive multi-step approach. Given the scattered nature of subcellular distribution information in the literature, we implemented a systematic literature mining strategy using PubMed and Google Scholar. Search queries were constructed by combining (i) individual DT names/synonyms with subcellular organelle names and (ii) generic terms ("drug transporter," "transporter protein," "transport") with organelle names. Retrieved publications were manually curated to extract experimentally validated proteomic expression data of DTs across different subcellular compartments. To complement experimental data, we employed the LocPro algorithm [49] to predict subcellular localizations based on protein sequences of experimentally validated DTs. This dual approach yielded a comprehensive dataset of 1034 subcellular distribution entries, comprising 593 experimentally validated records for 422 DTs across 68 organelle types, and 441 predicted entries for 316 DTs across 7 organelle types. To facilitate data interpretation, we generated separate visualization schemas depicting the subcellular distribution patterns for both experimentally validated and computationally predicted DT localizations (shown in Fig. 4). Figure 4A shows the results of the literature-based study, listing confirmed subcellular locations (e.g. apical cell membrane, mitochondrion), with each entry directly linked to its source publication. For intuitive interpretation, these validated localizations are also synthesized and visualized on a canonical cellular diagram. Figure 4B displays *in silico* prediction from the LocPro [49], presenting the most likely subcellular location(s) along with a quantitative confidence score for each. By juxtaposing curated experimental data with high-throughput predictions, this tool enables researchers to form more robust hypotheses about a transporter's physiological role and its contribution to drug disposition at the subcellular level.

Updating previously collected variability data of DTs

In addition to incorporating the three new aspects of distribution variability data detailed above, we have also updated the contents of our previous modules—"general variability (v1.0)," "structural variability (v2.0)," and "regulatory variability (v3.0)"—following the established methods for data collection and processing. The specifics of these updates are summarized in Table 1 and described below.

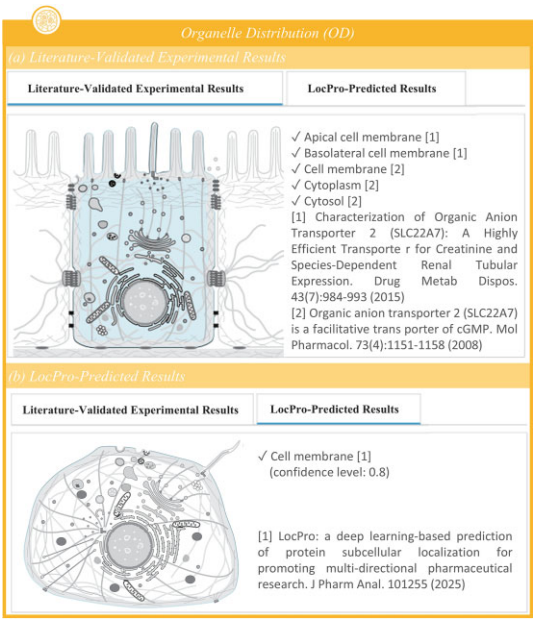

Figure 4. Subcellular localization of DTs. (**A**) Experimentally validated subcellular localization based on published literature. (**B**) Computationally predicted subcellular localization using LocPro.

For the general variability data, we have expanded the genetic variability information to include polymorphism type, polymorphic site on human chromosomes, minor allele frequency, affected drugs, corresponding disease susceptibility, and detailed associated phenotypes (e.g. drug response, survival, disease risk, and adverse reactions). In total, 10 045 Genetic Polymorphisms of drug transporter data entries for 118 DTs were collected. In the "Disease-specific Protein Abundances (DPAD)" section, we computed and integrated a total of 36 565 DPAD data entries, which encompass 82 new diseases and their corresponding 49 tissues. Furthermore, 36 628 box plots illustrating differential transporter expression between diseased and normal tissues, and 73 256 bar charts for normal and diseased tissues, were generated for comparative analysis.

Regarding the structural variability data, we obtained 37 mutation-induced spatial variations (MSV) entries for 20 DTs, determined by NMR spectroscopy, X-ray crystallography, and electron microscopy techniques. A total of 984 interspecies structural differences (ISD) data were added, comprising 170 structures involving 28 DTs from 8 model organisms (rat, mouse, zebrafish, cow, rabbit, fruit fly, and clawed frog), and 814 structures involving 130 DTs of human. We also obtained 160 new outward/inward-facing conformation (OIC) entries for 37 DTs, determined by experimental techniques.

For the regulatory variability data, we collected a total of 4 microbiota influence (MBI) data entries for 4 DTs regulated by one microorganism; added 949 post-translational modification (PTM) data entries for 184 DTs involving 12 PTM types; added 3928 transcriptional regulation (TSR) data entries covering 367 DTs regulated by 91 transcription factors; added 22 epigenetic regulations (EGR) data entries for 15 DTs; and added 24 812 exogenous modulation (EGM) data entries involving 402 DTs.

Table 1. Summary of updates to the variability modules and integration of distribution variability data

VARIDT versions	Variability	Data statistics	
		v3.0	v4.0
General variability (v1.0)	Genetic variability	1277	11 322
	Disease-specific protein abundances	42 978	79 543
Structural variability (v2.0)	Mutation-induced spatial variations	69	106
	Interspecies structural differences	522	1506
	Outward/inward-facing conformation	118	278
Regulatory variability (v3.0)	Microbiota influence	2068	2072
	Post-translational modification	10 255	11 204
	Transcriptional regulation	10 744	14 672
	Epigenetic regulation	39 779	39 801
	Exogenous modulation	12 276	37 088
Distribution variability (v4.0)	Tissue-level distribution	–	25797
	Cell-level distribution	–	451830
	Organelle-level distribution	–	1034

Conclusion and perspectives

VARIDT 4.0 is unique in describing (i) the first systematic integration of multilevel distributions of DTs, constructing a panoramic network from tissue level, then to cell level, and finally to organelle level; (ii) the compilation of subcellular localization data, revealing specific distribution patterns of DTs among many organelles; (iii) the high-resolution cellular expression heterogeneity mapping, identifying DT expression differences among various cell types within the same tissue; (iv) the comprehensive updating and expansion of our previous modules on general variability (v1.0), structural variability (v2.0), and regulatory variability (v3.0); and (v) the advanced interactive visualization, supporting the users in intuitive exploration of complex multidimensional DT distribution pattern. These unique features made VARIDT 4.0 an indispensable data source supporting drug transport research and drug design, and guiding personalized medication. VARIDT 4.0 is now accessible without login requirement at https://idrblab.org/varidt/.

In this major update of VARIDT, we have fundamentally enhanced the dimensionality and depth of the database. This integration ensures that the vast majority of core DTs are now annotated with unprecedented depth, with data coverage spanning from foundational genetic, structural, and regulatory features to their expression profiles across multiple biological scales.

The core contribution of this update, however, lies in providing a key platform for elucidating the mechanisms of "cross-scale interaction" that govern drug response. It is critical to emphasize that molecular attributes do not exist in isolation; their ultimate functional impact is realized through a complex spatiotemporal expression and interplay across multiple biological scales, from tissues and cells down to organelles [50]. For instance, a specific genetic polymorphism may subtly alter a transporter's conformation, increasing its susceptibility to proteasomal degradation. This degradation might be activated only within the lysosomes of a specific cell type (e.g. hepatocytes), ultimately leading to diminished overall clearance capacity in the organ (e.g. the liver) and causing drug-induced toxicity [51]. While each scale of data offers a unique perspective on drug response, it is the integration of these cross-scale interactions that forms the complete evidence chain linking a molecular event to a clinical phenotype. Such cross-level mechanistic investigations are increasingly recognized as essential in diverse biomedical contexts, ranging from modernizing the mechanistic basis of traditional Chinese medicine [52] to capturing metabolic plasticity in cancer progression and therapy resistance [53].

Therefore, by systematically combining multilevel distribution maps with in-depth foundational variability data for the first time, the new version of VARIDT provides a unique platform for researchers to systematically explore these cross-level mechanistic links. We believe this highly integrated, multiscale dataset not only provides a solid foundation for building next-generation systems pharmacology and PBPK predictive models but will also catalyze the generation of novel scientific hypotheses, shifting the research paradigm from analyzing single variations to systematically understanding their functional consequences. Looking forward, we are committed to continuously enhancing the database's integrative and analytical capabilities to provide critical support for the realization of truly personalized therapeutic strategies and the advancement of new drug discovery.

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Conflict of interest

None declared.

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Data availability

All distribution data of DT can be viewed, accessed, and downloaded from VARIDT, which can be freely accessed by all users at https://idrblab.org/varidt/.

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