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Database issue

DRESIS 2.0: the comprehensive landscape of drug resistance information

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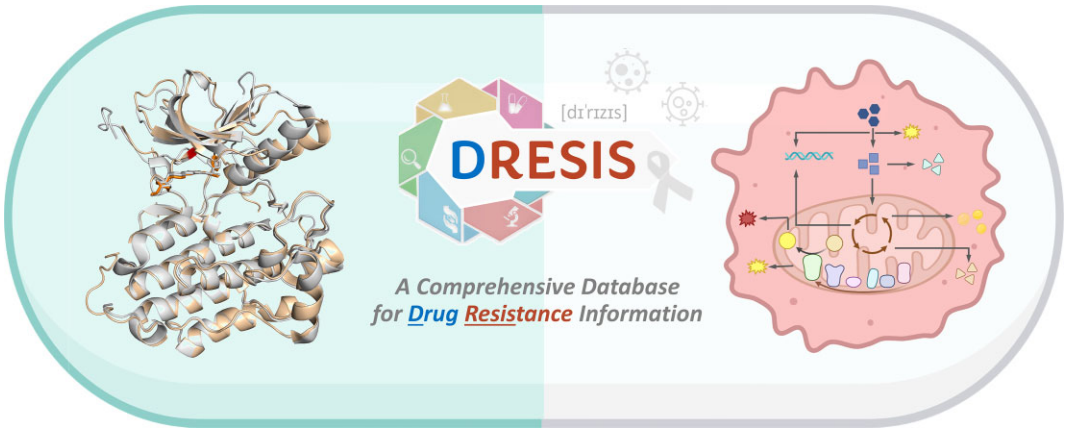
Abstract

Elucidating mechanisms of drug resistance is key for overcoming resistance, guiding drug design, and enabling accurate resistance prediction. Recently, *disease metabolic reprogramming* has emerged as a novel mechanism of resistance, which enables disease cells to adapt to therapeutic resistance by altering energy production pathways, cellular signaling, and biosynthesis processes. Moreover, *protein structure alterations* also play a pivotal role in resistance study, facilitating mechanistic understanding, and structure-based target discovery. In other words, integrating these recently accumulated critical data is essential for enriching the landscape of drug resistance data. Therefore, in this study, DRESIS was a significant update by providing (i) 236 molecules that drive metabolic reprogramming and confer resistance to 168 drugs, together with a detailed mechanism, (ii) 2228 protein structural variants implicated in resistance to 671 drugs across 238 diseases, and (iii) greatly expanded landscapes of drug resistance information, now featuring 398 newly added key drug-resistant molecules, 356 drugs with the latest published resistance mechanisms, and 81 new drug-resistant disease categories. All in all, DRESIS 2.0 is expected to serve as a valuable resource for the scientific community and provide important support in tackling the global challenge of drug resistance, which is now publicly accessible at https://idrblab.org/dresis/

Graphical abstract



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Introduction

Drug resistance poses increasingly serious threats to public health with devastating consequences [1–3], and DRESIS database was therefore constructed to provide multidimensional information for >20 000 drugs with either clinically reported or *in vivo*/cell line-validated resistance data [4]. The *disease metabolic reprogramming* (leading to the aberrant activations of metabolic pathways that produce amino acids, carbohydrates, etc.) has recently been recognized as a new but essential cause of disease-specific resistances [5–8], which is an indispensable piece of the puzzle enabling systematic investigation of the mechanisms underlying drug resistance [9]. Moreover, the *protein structure alterations* (including conformation variations in drug target, function modifications in drug transporter, metabolic abnormalities in drug-metabolizing enzyme, etc.) have attracted great research attention due to their critical roles in drug resistance [10–12], the understanding of which is thus valuable for the development of therapies helping to reverse drug resistance [13, 14]. With the rapid accumulations of research interests in the drug resistances induced by *disease metabolic reprogramming* and *protein structural alterations*, it is urgently demanded to have these recently accumulated critical data for enriching the landscape of drug resistance information.

Until now, several valuable databases related to the aforementioned topics have been constructed. Some of them depict the general drug resistance information for specific disease classes, such as CARD [15], CancerDR [16], Stanford HIV Database [17], and MARDy [18]. Some others describe the resistance information at single-cell resolution, such as DRMref [19] and ScDrugAct [20]. The remaining provide the relations between drug resistance and structure variation only as part of a broader collection of pharmaceutical information, such as MdrDB [21], mutLBSgeneDB [22], and Platinum [23]. However, the above critical resistance data (*disease metabolic reprogramming* and *protein structural alteration*) are not sufficiently covered by available knowledge bases.

Herein, an update of the DRESIS database was thus performed through describing the resistances induced by *disease metabolic reprogramming* and *protein structure alterations*. First, a total of 236 molecules driving the metabolic reprogramming resulting in the resistance of 168 drugs were accumulated from literatures, and the mechanisms for reprogramming many metabolic processes (such as *redox metabolism*, *carbohydrate metabolism*, *lipid metabolism*, *nucleic acid metabolism*, *mitochondrial metabolism*, and *amino acid metabolism*) were discovered and explicitly described. Second, a total of 2228 structural alterations (comparing the structures between resistance and wild type of 61 drug targets, 27 drug transporters, 62 drug-metabolizing enzymes, and 45 proteins essential in disease pro-survival pathways) were systematically collected. These alterations underlined the resistance mechanisms for 671 drugs in treating 238 indications from 142 disease classes defined by latest WHO *International Classification of Disease* ICD-11 [24]. Third, the existing landscape of drug resistance in initial DRESIS was substantially expanded by (i) providing disease-specific differential expression data for 539 resistance-related molecules that were not previously covered by DRESIS (from 704 to 1243); (ii) collecting the recently published mechanism underlying the resistances of 184 approved, 102 clinical trial, and 70 investigative drugs; and (iii) enabling a customized data browse using seven types of resistance mechanisms and the structures of reprogrammed molecules. DRESIS is accessible without login requirement by users at https://idrblab.org/dresis/

Factual content and data retrieval

Systematic accumulation of drug resistance information

The data of drug resistances induced by *disease metabolic reprogramming* and proteins' structure variation underlying each drug resistance were collected by the following processes. For *the data of disease metabolic reprogramming*, literature review was performed in PubMed using keyword combination searches, such as '*metabolic reprogramming + drug resistance*,' '*glucose metabolism + drug resistance*,' '*metabolic mechanism + drug resistance*,' '*Warburg + drug resistance*,' and '*lipids metabolism + drug resistance*.' As a result, a total of 236 key molecules driving metabolic reprogramming leading to the resistances of 168 drugs were collected. Then, the mechanisms for reprogramming diverse metabolic processes (*mitochondrial metabolism*, *redox metabolism*, *lipid metabolism*, *amino acid metabolism*, *carbohydrate metabolism*, *nucleic acid metabolism*, and so on) were retrieved from the discovered papers. Finally, the affiliated data of disease and molecule were accumulated, including drug synonym, indication name, ICD-11 classification, etc.

For *the structure data underlying drug resistances*, the structures of wild-type or mutant resistant molecule were collected by searching the names/synonym of all resistance molecules in PubMed and PDB [25] using such keyword combinations as "*mutation + drug resistance*," "*mutant molecule + drug resistance*," etc. Additionally, those structures of wild-type protein could be identified by blasting the full-length protein sequence against all PDB sequences. A subset of mutant structures derived from sequence alignment, together with the associated ligands, were further incorporated. Only the PubMed literature or PDB entry that explicitly showed the structure of wild-type/mutant was collected into DRESIS 2.0. Then, for the resistance molecule absent of known PDB mutation site, its structure was predicted using the locally deployed AlphaFold3 model [26]. According to mutation information, the wild-type sequence was modified to produce the corresponding mutant sequence and subjected to structure prediction by AlphaFold3. Finally, the structure information was accompanied by experimental details. The reliability of AlphaFold3-predicted structure was assessed using pLDDT and *Predicted Aligned Error*. For each wild-type or mutant molecule pair, the degree of protein structure deviation was quantified using root mean square deviation (RMSD) and TM-score.

Resistance induced by disease metabolic reprogramming

It is imperative to uncover the mechanisms underlying each drug resistance [27–29], and six well-established ones have been documented in DRESIS. Recently, *disease metabolic reprogramming* was widely recognized as one of the key mechanisms driving drug resistance [30, 31]. Particularly, existing studies discovered that in *non-small cell lung cancers*, the high expressions of branched-chain amino acid transaminase 1 can activate glycolysis through epigenetic mechanisms, leading to the resistances of third-generation EGFR-TKIs [32]. Additionally, substantial evidence further highlights the key roles of

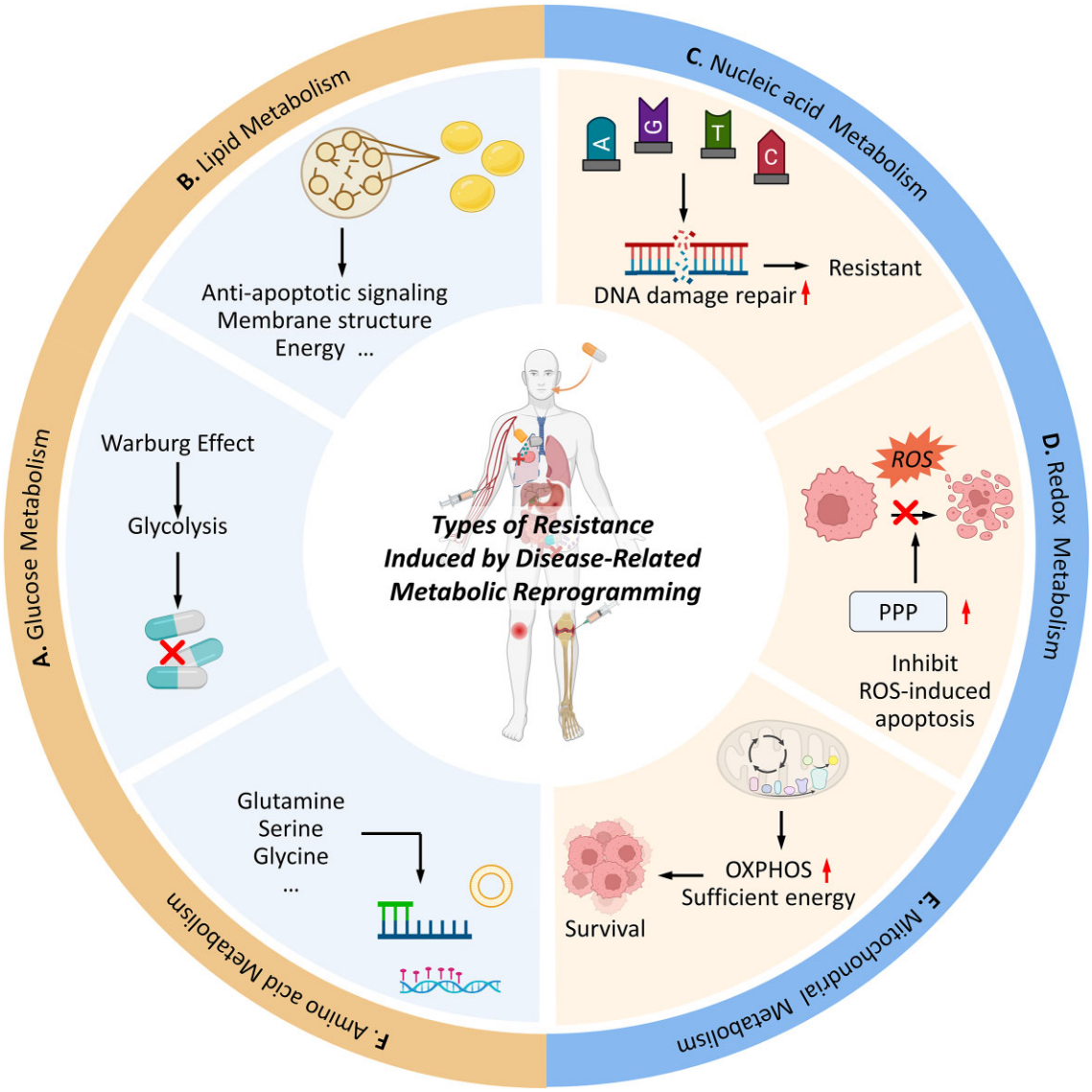

Figure 1. A schematic illustration of the six key metabolic types of metabolic reprogramming in the development of drug resistance, including *glucose metabolism, amino acid metabolism, lipid metabolism, mitochondrial metabolism, redox metabolism,* and *nucleic acid metabolism*. Particularly, (**A**) tumor cells often favor aerobic glycolysis (the Warburg effect) to fuel rapid proliferation. (**B**) Lipid metabolism promotes survival by regulating anti-apoptotic signaling, membrane integrity, and energy generation. (**C**) Nucleic acid metabolism supports chemoresistance through *de novo* purine and pyrimidine synthesis, facilitating DNA repair. (**D**) Redox balance is maintained via enhanced pentose phosphate pathway activity, mitigating ROS-induced apoptosis. (**E**) Chemotherapy can induce a shift to oxidative phosphorylation, enabling ATP-dependent survival. (**F**) Reprogrammed amino acid metabolism further influences drug efficacy through biosynthesis, redox homeostasis, and epigenetic mechanisms.

sustained upregulation of aerobic glycolysis in resistance development [33, 34]. The metabolic reprogramming refers to the systemic and lasting adjustment of metabolic pathways, metabolite utilization, and energy supply patterns in response to new physiological or pathological demands in disease [35]. Notably, cells reshape the intake, synthesis, and breakdown of nutrients (*glucose*, *fatty acid*, *amino acid*, etc.) to meet the key needs of abnormal proliferation, survival, migration, or adaptation to the environmental stress [36]. Existing research has revealed that metabolic reprogramming is closely associated with the onsets and progressions of resistances [37], involving many metabolic processes (as shown in Fig. 1, like *glucose metabolism*, *amino acid metabolism*, *lipid metabolism*, *mitochondrial metabolism*, *redox metabolism*, and *nucleic acid metabolism* [38–42]). Such adaptation was usually mediated by various signaling pathways, such as MEK/ERK [43], Notch [44], NF-κb [45], and PI3K/AKT/mTOR [46], thereby promoting cancer cell survival and contributing to resistance development [47]. Considering the finding, there is a need to consolidate and disseminate data regarding metabolic reprogramming in drug resistances. The curation and provision of such data in DRESIS 2.0 is thus key for advancing the understanding of resistance mechanisms and improving the strategy for drug clinical development [48].

In DRESIS, a detailed description of drug resistance induced by *disease metabolic reprogramming* was systematically depicted. As shown in Fig. 2, general pharmaceutical information of drugs, diseases, and key molecules was provided in the upper section, which included *Drug Name*, *Drug Synonyms*, *Disease Indications* with corresponding clinical sta-

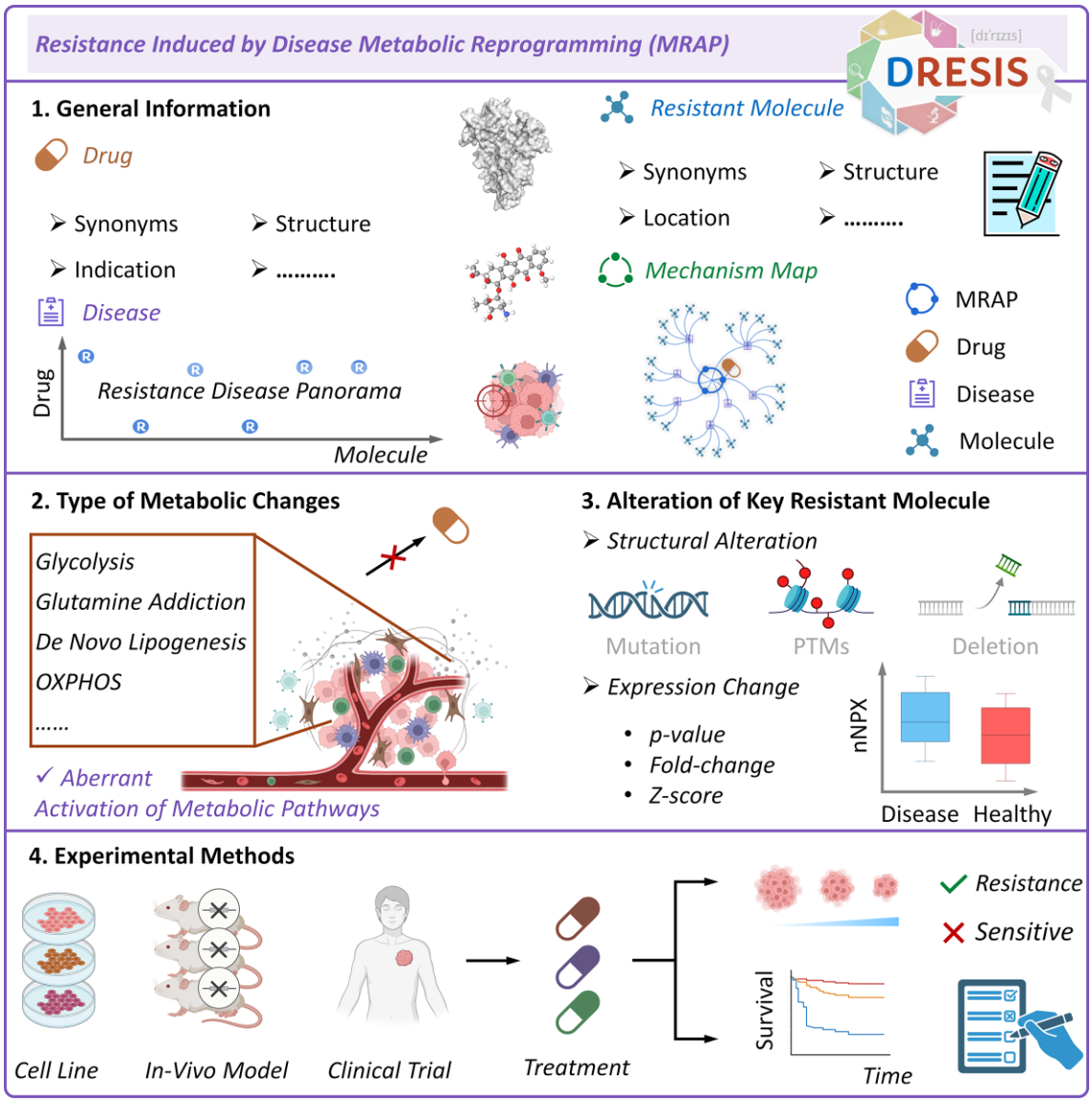

Figure 2. The typical page for depicting resistance induced by *disease metabolic reprogramming*. (**1**) The general pharmaceutical information of drugs, diseases, and key molecules was separately described including: *Drug Name and Synonyms*, *Disease Name and Resistance Panorama*, *Molecule Name and Synonyms,* etc. (**2**) Detailed information on metabolic reprogramming-mediated drug resistance was explicitly provided for each studied drug, along with the corresponding list of associated diseases. The underlying resistance mechanisms were further explicitly elucidated by classifying each resistance case according to six metabolite types (including *glucose*, *amino acid*, *lipid*, *mitochondrial*, *redox*, and *nucleotide metabolism*). (**3**) The detailed alterations of key molecule were documented, including the *structural alterations* and *variations in molecule expression*. (**4**) Diverse types of resistance evidence and a wide range of experimental details were explicitly illustrated including the diverse experimental techniques, hundreds of disease cell lines and *in vivo* models, and relevant signaling pathways.

tus, *Drug Structures*, *Drug Targets*, *Disease Name*, *Resistant Disease Panorama*, *Resistant Molecule and its affiliated data*, and so on. Additionally, the detailed information on metabolic reprogramming-mediated drug resistance for each drug together with the corresponding disease list was provided in Fig. 2. The underlying resistance mechanisms were also depicted by classifying each resistance according to metabolite types (*glucose metabolism*, *amino acid metabolism*, *lipid metabolism*, *mitochondrial metabolism*, *redox metabolism*, and *nucleotide metabolism*). For each drug, multiple diseases are usually found with reported resistance, and these diseases were classified according to their resistance evidence (*clinically reported*, *validated by in vivo model*, and *discovered using cell line experiment*). Notably, the resistance of drugs was associated with different complex metabolic pathways.

The alteration detail of resistant molecules was also provided, including the structural alterations (such as those induced by mutation, deletion, or post-translational modification) and the variation in expression profile. Additionally, the resistance evidence and experimental details were shown in Fig. 2, including diverse experimental techniques (such as CCK8 assay, LC-MS assay, and flow cytometry assay), various disease cell lines (such as JHH1, PC-9, and SUDHL2), distinct *in vivo* models (like NCI-H1975 xenograft-bearing mice, MIER2 overexpressing mice, and BALB/c nude mice), and many signaling pathways (PI3K/AKT, TGF-beta, mTOR,

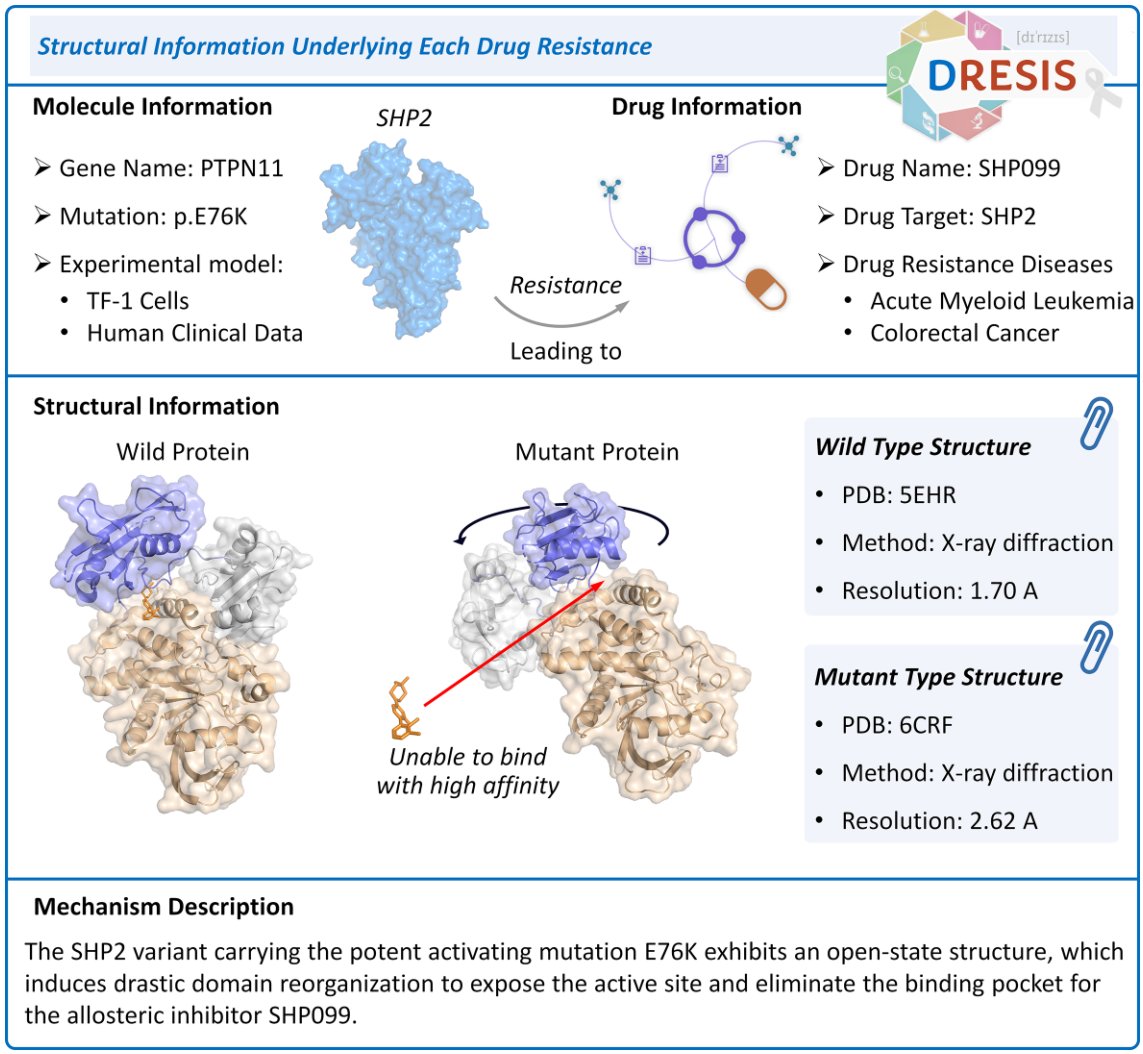

Figure 3. The typical page for depicting the detailed protein structural information underlying each drug resistance. Taking the protein SHP2 as an example, the SHP2 variant carrying the strongly activating E76K mutation undergoes substantial domain reorganization, resulting in an open conformation distinct from the wild type. In other words, the conformational change causes the disruption of the SHP099 binding pocket, which in turn impairs high-affinity binding and ultimately reduces the inhibitory potency of SHP099. Apart from the structural alterations, a variety of experimental details were also provided, which included diverse experimental methods (such as X-ray diffraction, electron microscopy, solution NMR, and so on), structure resolution, and types of resistance evidence (such as clinically reported, validated by an *in vivo* model or identified using a cell line experiment), and so on.

etc.) that are regulated in resistance diseases were also identified and provided online. All in all, a total of 236 molecules driving metabolic reprogramming resulting in the resistances of 168 drugs were systematically accumulated from publications, and their corresponding mechanisms for reprogramming diverse metabolic processes were identified and explicitly described in the latest DRESIS database.

Protein structural information underlying each drug resistance

Protein structural alterations (like conformation variations in drug targets, function modifications in drug transporters, metabolic abnormalities in drug-metabolizing enzymes, etc.) are found crucial in determining drug resistance [49–55]. For instance, MEN1 mutations confer clinical resistances to the inhibition of MEN1 by disrupting drug binding and preventing displacement of the MEN1–MLL1 complex [56]. In the 1.0 version of DRESIS, over half of the resistance mechanisms were attributed to structure alteration. Such structured data are key for clarifying resistance mechanisms, guiding drug design, and predicting cross-resistances, thereby offering indispensable insights for resistance studies and clinical researches [57–60]. Particularly, such data could help to understand the resistance of antiviral drugs by studying the interaction between HSV polymerase and human DNA [61], which further support the development of antifungal drugs by elucidating the structure and mechanism of β-1,3-glucan synthase FKS1 [62] and inform clinical strategies for lung cancer patients harboring EGFR mutations through drug sensitivity predictions [63]. In other words, the collection of structural data was essential for advancing research on drug resistance [64–69].

In this analysis, a total of 2228 structure variants between mutant and wild-type proteins are thus collected, including 61 drug targets, 27 drug transporters, 62 drug-metabolizing enzymes, and 45 key proteins promoting disease survival pathway. As depicted in Fig. 3, the detailed protein structural information underlying each resistance was explicitly provided.

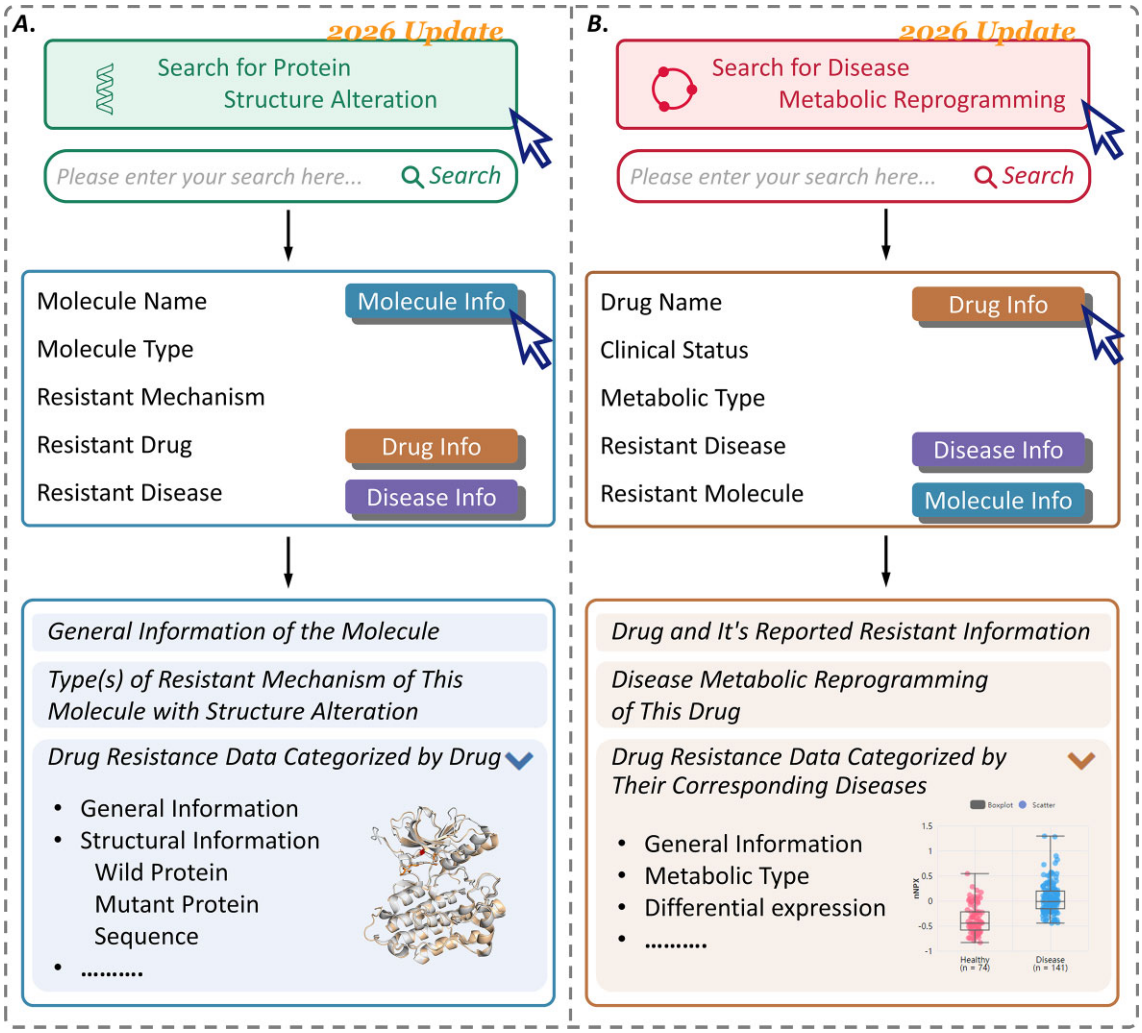

Figure 4. The updated features of DRESIS 2.0 allow users to select from the following modules for querying: (**A**) Search for Protein Structure Alteration or (**B**) Search for Disease Metabolic Reprogramming. Once a module is chosen, users need to enter relevant drugs, diseases, or molecules to perform the search. The results will be presented as interactive cards. Moreover, users can click on "Molecule Info," "Drug Info," or "Disease Info" to access detailed drug resistance information for more in-depth data.

Taking SHP2 as an example, its structure data for both wild type and mutant were shown in DRESIS 2.0. Particularly, SHP2, encoded by PTPN11 gene, plays a key role in multiple tumor-related signaling pathways [70], including RAS-RAF-ERK, PI3K-AKT, JAK-STAT, and NF-κB [71]. It consists of four parts: two tandem SH2 domains (N-SH2 and C-SH2), a catalytic protein tyrosine phosphatases (PTP) domain, and one C-terminal region [72]. Under physiological conditions, wild-type SHP2 adopts a closed conformation in which N-SH2 domain occupies the catalytic pocket of the PTP domain, thereby sterically hindering the active sites. The allosteric modulator SHP099 stabilizes this closed state, but mutations can compromise its inhibitory efficacy. For instance, as illustrated in Fig. 3, the SHP2 variant carrying activating E76K mutations undergoes substantial domain reorganizations, resulting in an open conformation distinct from the wild type. In other words, the conformational change results in the disruption of SHP099 binding pockets, which in turn impairs high-affinity binding and ultimately reduces the inhibitory potency of SHP099 [73]. Apart from the structural alterations, various experimental details were provided, which included diverse experimental methods (such as X-ray diffraction, electron microscopy, solution NMR, and so on), structure resolution, and types of resistance evidence (such as clinically reported, validated by an *in vivo* model, or identified using a cell line experiment), and so on. All in all, the protein structural information underlying each drug resistance were established in DRESIS 2.0, and the resulting data were well organized for access and downloading by users.

Significant update of drug resistance data in DRESIS 1.0

The existing landscape of drug resistance information in the first version of DRESIS was substantially expanded. Specifically, (i) the disease-specific differential expression data were provided for 539 new key resistance molecules that were not covered in DRESIS 1.0, increasing from 704 to 1243; (ii) the recently published mechanism underlying the resistance of 184 FDA approved, 102 clinical trials, and 70 investigative drugs was systematically collected; and (iii) a customized browse of resistance data based on seven different types of resistance mechanisms and the structures of reprogramed molecules was enabled. All in all, the number of

drug-resistance disease classes included in DRESIS 2.0 has increased from 395 to 476, and the number of drug-resistant molecules has increased from 2254 to 2652, representing a significant enrichment of both the breadth and depth of the database.

Description of website page for DRESIS 2.0 usage

Users can explore the *protein structure alteration* and *disease metabolic reprogramming* modules by selecting the corresponding options under the "2026 Update" section on the homepage, as shown in Fig. 4. In the "*Search for Protein Structure Alteration*" module (as illustrated in Fig. 4A), users can enter a relevant "drug name," "molecule name," or "disease name" for querying. Upon clicking the "Molecule Info" option, the search results will display the resistance information about this molecule, including its general information and the type(s) of resistance mechanisms associated with structural alterations. Specifically, the results will present drug resistance data categorized by specific drugs, as well as structural information, which includes both wild-type and mutant protein sequences. More detailed resistance information regarding the molecule's structure and its associated resistance mechanisms will also be provided. Additionally, users can click on "Drug Info" or "Disease Info" to access comprehensive drug resistance information for further details.

Similarly, in the "*Search for Disease Metabolic Reprogramming*" module (as offered in Fig. 4B), users can enter a relevant "drug name," "molecule name," or "disease name" for querying. Upon selecting the "Drug Info" option, the results will display the drug and its associated resistance information induced by disease metabolic reprogramming. Specifically, the results will present drug resistance data categorized by corresponding diseases, as well as general information, metabolic type (such as *glucose metabolism*, *amino acid metabolism*, *lipid metabolism*, *mitochondrial metabolism*, *redox metabolism*, and *nucleotide metabolism*), differential expression of the resistant molecule (as shown in a boxplot scatter), and so on. In other words, detailed resistance information caused by *Disease Metabolic Reprogramming* will be provided to help identify drug-resistance patterns related to metabolic changes in diseases. Moreover, users can click on "Molecule Info" or "Disease Info" to access comprehensive drug resistance information for further details. All in all, this visual presentation enables interactive exploration of resistance patterns, thereby enhancing user engagement and facilitating more intuitive access to resistance-related data.

Data statistics, standardization, access, and retrieval

To make the access and analysis of DRESIS 2.0 data convenient for all readers, the collected raw data were carefully cleaned up and then systematically standardized. These standardizations included: (i) cross-linking all newly added drugs, diseases, key drug resistance molecules, cell lines, and protein structures with established databases and (ii) standardization of all newly added disease indications according to the *International Classification of Diseases* (ICD-11) officially released by the World Health Organization [24]. Furthermore, a user-friendly interface was created by our database to enable convenient browse and search of data. All drug resistance data could be viewed, accessed, and downloaded from DRESIS 2.0, which could be freely accessed without login requirement at https://idrblab.org/dresis/

Conclusion and prospect

Understanding the mechanisms underlying drug resistance is essential for addressing the widespread and severe challenge of resistance. The initial version of DRESIS systematically documented six classical mechanisms together with extensive resistance information. With advances in research, metabolic reprogramming has emerged as an additional mechanism of resistance. In this study, the resistance mechanisms driven by metabolic alterations were systematically collected, thereby facilitating the development of therapeutic strategies targeting metabolic processes. Moreover, DRESIS 2.0 incorporates protein (i.e. wild type and mutants) structural information, which has attracted great research attention due to their critical roles in drug resistance and is expected to support drug design and resistance prediction. Therefore, DRESIS 2.0 expands the database by incorporating these two new sections while also updating original dataset. Altogether, this enriched resource will provide valuable support for overcoming the serious problem of drug resistance in the clinic application.

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Conflict of interest

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Data availability

All drug resistance data can be viewed, accessed, and downloadable from DRESIS 2.0, which is freely accessible without any login requirement by users at: https://idrblab.org/dresis/.

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