Common Features in Substrates of Multidrug Resistance Transporters

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1 Introduction

Multidrug resistance (MDR) proteins serve as transporters for chemical compounds, small molecules like antibiotics in almost all species from bacteria to higher eukaryote. They provide the resistance against antibiotics and chemicals for the cells like cancer, fungi and parasite, etc. Therefore, the research on MDR proteins is essential and important in medical, agricultural and scientific fields. Five transporter families are known to contain MDR members as follows. ABC (ATP-binding cassette superfamily), MFS (major-facilitator superfamily), SMR (small multidrug resistance family), RND (resistance-nodulation cell division family), and MATE (multidrug and toxic compound extrusion family). The ABC transporter consists of some subfamilies, such as pgp, mrp and pdr. The ABC transporter is driven by ATP hydrolysis energy, and the other four families are driven by proton/sodium motive force. It was reported that more than 90% of MDR genes are composed of ABC and MFS genes in completely sequenced bacteria genomes [4]. In general, the relationship of the transporter and its substrate is highly specific, but MDRs are known to be transporters that have broad spectrums of drugs and chemical compounds. Thus, MDRs are poly-specific rather than non-specific transporters [5]. Many substrates have been found and used in experiments for characterizing properties of MDRs. The spectrum of each MDR family is known to be somewhat distinct, but the relationship to the structural and physicochemical properties of substrates has not been well established. Previously, we collected chemical compound structures for substrates of MDR proteins from the published literature and tried to retrieve structural and physicochemical properties [2], They were represented by 67 kinds of the KEGG atom types [1]. In this study, we classified these collected chemical compound substrates and extracted common sub-graphs of them by using Vzyme [3] in order to detect putative recognition sites in chemical compound substrates by the MDR protein.

2 Methods

The detection of common subgraphs in pairwise chemical compound structure comparison was performed by the Vzyme, and its output similarity scores were used as distances in the Ward clustering analysis. The Vzyme system was developed by Okuno et al [3] for predicting whether one compound is likely to be converted to the other by an enzymatic reaction, which is based on the search against the reaction template library. The Ward method is one of the hierarchical clustering analyses, and is in a manner that minimizes the loss associated with each grouping. At each step in the analysis, the union of every possible cluster pair is considered and the two clusters whose fusion results in the minimum increase in information loss are combined. Information loss is defined by Ward in terms of an error sum-of-squares criterion.

3 Results

In the result of the hierarchical classification of chemical substrate compounds which are transported by 5 kinds of MDR protein families, we obtained three large chemical compound substrate groups as follows: (I) specific skeletons with low proportion of aromatic rings or sugars, (II) linear molecules like peptides and glutathiones, (III) compounds which have high proportion of aromatic rings or low molecular weights. Moreover, these three large groups were categorized into 12 clusters with the following chemical terms: 1) sugar skeletons, 2) beta-lactam skeletons, 3) steroid skeletons, 4) non-aromatic rings with sugars, 5) quinolones, 6) peptides, 7) linear molecules, 8) glutathione and its derivatives, 9) highly charged compounds, 10) low molecular weight compounds, 11) aromatic ring and 12) chrysin skeletons, as illustrated in Fig.1. In this analysis, some chemical compound substrates with specific frameworks, like steroids and beta-lactams, fell on individual clusters. On the other hand, there are several compound clusters which are not represented by restricted chemical structures, but are found to contain other features, such as low molecule weights or high proportions of aromatic rings, etc.

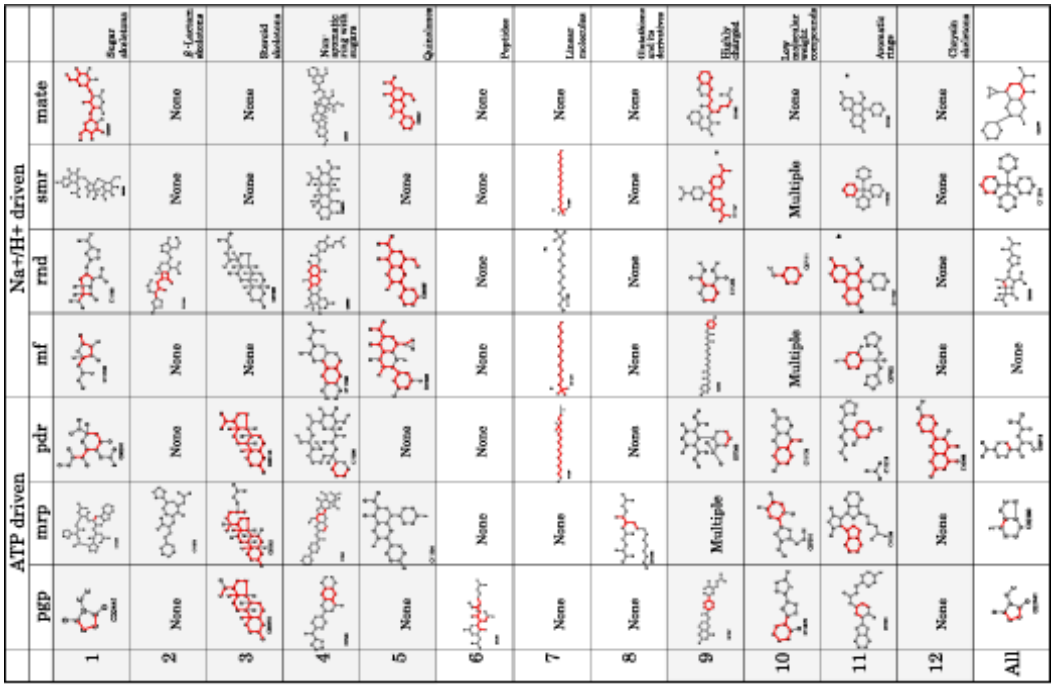

Figure 1: Representative chemical compound substrates in individual clusters.

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