SindhUniv. Res. Jour. (Sci. Ser.) Vol. 52 (01) 85-92 (2020)

http://doi.org/10.26692/sujo/2020.03.13

SINDH UNIVERSITY RESEARCH JOURNAL (SCIENCE SERIES)

Emergence of major drug resistant transport family Conserved proteins in fungi

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Received 08th July 2019 and Revised 6thJanuary 2019

Abstract: Fungal genome have highest number of the ATP binding cassette (ABC) superfamily PDR (Pleotropic drug resistance) sub divided into MDR (multi drug resistance) and MFS (major facilitator family). The major conserved domain of the super family comprised of various alpha helix proteins in form of ATP binding cassettes as transmembrane. Another conserved (NTP) nucleotide binding domain contained of conserved amino acids is more crucial domain of super family. ABC proteins are majorly involved in transport across cytoplasm and plasma membrane for the number of substrates as proteins, amino acids, ions and drugs. According to the recent studies yeast and *Neurosporacrassa*have highest number of orthologs and is the best model to uncover the underlying phenomena of drug resistance for the better understanding. There is dearth of study on the existence of drug transport proteins in pathogenic fungi. Study have focused on the emergence of CDR, MDR and MRS family major drug resistant transport proteins in various fungal groups.

Keywords: *Neurosporacrassa*, major conserved domain, ATP binding cassettes, ABC proteins, Drug resistance.

1. INTRODUCTION

Fungal genome has various ATP binding proteins that localized in plasma membrane, cellular vacuoles, mitochondria and peroxisomes. They majorly are involved in conferring resistance to the multitude drugs and the underlying phenomena is known as Pleiotropic drug resistance or MDR multidrug resistance (Wolfger, *et al.*,2004). Drug transporter pleiotropic drug resistant efflux pumps (PDR*)* family consisted of ATP binding cassette that require to influx the variety of compounds across the bio membranes. The expression profiles of the PDR family proteins are widely involved in drug resistance in plants and clinical samples. Fungi, plants and human ABC based PDR family contain two major binding domains, nucleotide binding domain (NBD) and trans membrane domain (TMD). ABC pumps contain NBD (domain) and depend on the ATP for energy release by hydrolyzing, while major facilitator superfamily MFS having (TMD) domain depend on the electrochemical gradient across the membrane (Cowen, *et al.*, 2000). MFS transporters comprised of 17 families (Akache, and Turcotte. 2002). ABC transportershave been studied in various microbial groups. Functionally they are majorly involved in transport for the range of the substances with the cytoplasmic NBD and membrane connected TMD domain as a functional unit. Azoles are the most frequently used antifungal and its increasing resistance in organisms is an upcoming challenge. The molecular mechanism of the reduced azole sensitivity is comparatively complex mechanism which is under the control of ergosterol biosynthesis enzymes and acquire resistance by several factors including up regulation of the multidrug ABC transporters encoded by CDR1 and CDR2 in *candida albicans* and the major facilitators (MDR1) (Sipos and Kuchler 2006). In genetic model species *Sacchromycess cerevisiae,* up regulation of the genes is coordinated by PDR5 and SNQ2 that encode ABC transporters are intervene by Pdr1 as well as pdr3 transcriptional profiles, that are comprised of large member family having zinc binding domain (Zn2Cys6) (Rogers *et al.*, 2003). (Chang *et al.*, 2004) (Schoonbeek *et al.*, 2003). (De Waard, *et al.*, 2006). Both of the proteins have CGG triplet direct repeats contained by their promoters (Rogers *et al.*,2003).(Schoonbeek*et al.*, 2003). It is suggested that *Aspergillus* species have 45 ABC transporters encoding genes in the genome. The ABC transporters superfamily generally known the key efflux transporters is classified into five groups e.g. ABCA, ABCB, ABCC, ABCD and ABCG where ABCB, ABCC and ABCG involved in the efflux of the toxic substances (Posteraro *et al.*, 2003) Prasad *et al.*, 1995). Another superfamily MFS transporter containing 12 spanning members of orthologs revealed less virulence in the host and the function of the most of efflux pumps associated with secondary metabolites is not clearly understood. The expression profiles of the MFS transporters for secondary metabolites genes are controlled by various transcription factors (Torelli *et al.*, 2008) (Katiyar, 2001). However in ABC transporters for

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the toxic substances TRI12 (Trichothecene T-2) toxins contains conserved sequences at the promoters for binding of transcription factors that suggestively controlled by the same gene cluster (Smriti, *et al.*,2002)

Expression profiles and Multitude functions

Numbers of PDR family transporters have been recognized as virulence factor. Toxic compound as phytoalexins identified as the expression inducers for the efflux transporters belonging to PDR and ABC family (Shukla, *et al.*, 2007) Fungal transporters MFS are also identified in the tolerance of phytoalexins (Pasrija *et al.*,2007) There are 21 ABC and 85 MFS encoding transporters identified in the genome of pathogenic fungi *Candida albicans.* ABC transporters belong to the vacuolar transportation that is acquired complete virulence in *C. albicans* (Calabrese *et al.*, 2000). There are various numbers of transporters in *C. albicans* such as, CDR1, CDR2, in *C. neoformans* AFR1, *C. glabrata* CgCDR1 etc. involved in cross resistance belong to the PDR family (Wirsching *et al.*, 2001) However, studies on CDR1 and CDR2 orthologous in pathogenic fungi identified their function as transporters of steroids and the phospholipids in the bio membrane (Coste *et al.*, 2004). In azole exposureCDR2 mutant in the exposure of fluconazole showed wild type similarity while double mutant of CDR2/CDR1 revealed sensitive phenotype to the fluconazole which predicted the CDR potential involvement in fluconazole exposure (Banerjee, *et al.*, 2020). On the biochemical basis CDR1 and CDR2 have high level of similarity of amino acids but had functional differences. ABC transporters have multiple substrates and substrate binding sites which takes place at different active sites as mentioned in **(Fig. 1).**

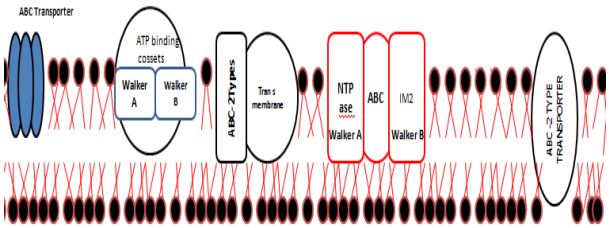

Fig.1 CDR family conserved domain

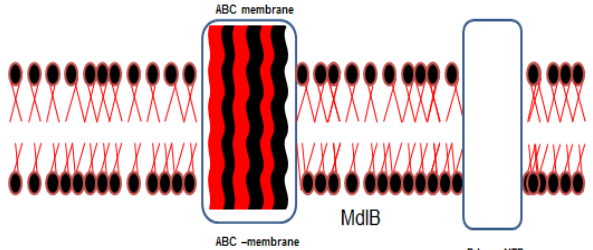

Fig.2 MDR (multi drug resistant) super family

Besides, ABC transporter another subfamily (Major facilitator super family) MFS and Multi drug resistance MDR transporters are also involved in fluconazole resistivity as MDR1, that have homolog in *C. albicans, C. dubliniensis* and *C.tropicalis*(Bhattacharya, *et al.*, 2019).MFS transporters TMP1 and TMP2 have been reported to confer resistance with various antifungals (Bhattacharya, *et al.*,2019).It is said that the drug responsive elements (promoter) of CDR1 and CDR2 act like Zinc and Cystein(Rogers *et al.*,2003) based transcription factor contributes to the resistance. Azole resistant genes are isolated to be carrying an extra chromosomal copy with CDR1and CDR2 but do not effect on the transcriptional levels of the gene and conform the fact that the transcriptional levels are effected due to the promoters or either the trans acting factors of the CDR genes (Banerjee, *et al.*,2020). In resistant isolates the duplication of TAC1 protein residing place is identified with the rearrangement of the second chromosome (Morschha, *et al.*, 2007) Moreover MRR1 zinc finger transcription factor was reportedly involve in the over expression of the MFS where by the homozygosity of the matting site was potentially involved in revealing the azole resistance in clinical isolates (Morschha, *et al.*, 2007).

Pleiotropic drug resistance (PDR family)

PDR family is the most studied and largest subfamily has two ABC proteins pdr5 and Snq2 situated in the membrane that confer resistance to various drugs on over expression.(Morschha, *et al.*,2007).However, Aus1 and PDR11 are implicated to transport the sterol to the cell (Ernst, *et al.*, 2008). The superfamily On the base of (*"CDD: NCBI's conserved domain database)* in CDR have two walker A and walker B domain linked with ATP binding cassette and NTP domain as shown in **(Fig.1).** In order to explore the more on Pdr it require to characterize the other members. *Saccharomyces cerevisiae* genome have 30 ABC transporter encoding proteins which further have been divided into five subfamilies as PDR, MDR, CFTR, ALDP and YEF3/ RL1, which are briefly describe as pleiotropic drug resistant ,multi drug resistant protein, cystic fibrosis transmembrane conductance regulator, adrenoleuko dystrophy protein and yeast elongation factor 3/RNase L inhibitor1 (Subfamilies).

Multidrug resistance family protein (MDR)

Conserved domain of MDR mainly consists of 6 ABC transmembrane helix and a P-loop NTPases uperfamily as shown in **(Fig. 2).** MDR superfamily has 36 highest numbers of orthologs in *Candia albicans* while, 20 and 8 in *Neurosporacrassa* and *Aspergillus fumigatus* among fungi. MDR family comprised on four sub proteins situated in the plasma membrane, where Atm1, Mdl1, Mdl2 and Ste6 localized around the

plasma membrane in yeast. WhereMdl1 export the peptides while Mdl2 function is unknown, atm1 is particularly involved in iron metabolic regulations (Saini, *et al.,* 2005). However, the Atm1, Mdl1 and Mdl2 are localized in inner membrane of the mitochondria.MRP/CFTR is the major member of the PDR family have ABC domain with additional ABC-MRP domain and P-loop NTPase motif as **(Fig.3).** Superfamily consisted of 83 highest number of orthologes in *N.crassa*and 82, 34 and 21 in *Saccromycescerevisae* and *Candida albicans*and *Aspergillus spp*. respectively. Moreover, MDR family share similarity to YOR1 protein of yeast act as Cl^- channel which on defection cause cystic fibrosis (Banerjee, *et al.,* 2020).ALDP proteins comprise of partial transporters namely Pxal1 and Pxal2 localized on the proximal membrane can uptake long chain fatty acids (Saini, *et al.,* 2005). The transcriptional upregulations of cdr1 and cdr2 have been studied in various azole resistant *Candida* isolates. Moreover the over expressed strain of *Candida neoformans* showed reduced acidification that has a connection with azole virulence studies observed in *Candida glabrata* azole resistivity(Puri, *et al.,* 2009)

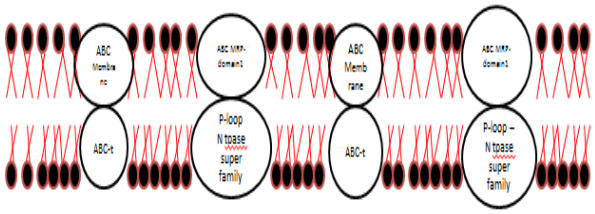

Fig.3 MRP conserved domain.

Drug transporters in Pathogenic fungi

Drug transporters are vital to transport the drugs across the membrane. Studies on clinical isolates in *C. glabrata* showed the upregulation of CDR1 and PDH1 including multi drug transporters in antifungal drug resistance. However, ERG11 coding sequences mutations are also involved in fungal resistance. The function of ABC transporters in azole exposure is mostly involved in resistance as Colchicine resistance with various carcinomas ubiquitously in the membrane. ABC cassettes comprised of transmembrane domains with highly conserved amino acid based proteins as nucleotide domains. They are most widely spread proteins in prokaryotes and eukaryotes act as a transporters, receptors and considered more crucial in cellular homeostasis. Aspergillus Species among the primary pathogens in filamentous fungi associated with high morbidity and drug resistance (Banerjee, *et al.,* 2020).The emergence of drug resistance among pathogenic fungi is considered an evolutionary step increased with the increasing exposure of the antifungal agents (Saini, *et al.,*2005).. However, the occurrence of the resistance due to functional mutation is also an established phenomenon. In *Aspergillus spp* the occurrence of multidrug resistance is usually caused by the reduced accumulations of the sterol intermediates that correlate with increased expression of the MDR genes of ABC and the MFS superfamily (Saini, *et al.*, 2005).

Table 1.CDR 1 homolog proteins in fungi.

Eurotiomycetes			*Saccharomycetes*		Schizosaccharomycetes		*Sordariomycetes*	
Gene	**Species**	**Homologs**	**Species**	**Homologs**	**Species**	**Homologs**	**Species**	**Homologs**
CDR1	*Aspergillus Fumigatus*	2	*Candida albicans*	22	*Schizosaccharomycesoctosporus*	1	*Fusarium verticillioi-des*	1
	Aspergillus Terreus	1			*Schizosaccharom-ycespombe*	1	*Magnaprtheoryzae*	1

Table 2.CDR 2 homolog proteins in fungi.

	Saccharomycetes		*Schizosaccharomycetes*	
Gene	**Species**	**Homologs**	**Species**	**Homologs**
CDR2	*Candida albicans*	17	*Schizosaccharomyces japonicus*	1
			Schizosaccharomyces octosporus	1
			Schizosaccharomyces pombe	1

Table 3.CDR 3 homolog proteins in fungi.

CDR3	*Saccharomycetes*		
	Accesion number	**Species**	**Homologs**
	SC5314	*Candidaalbicans*	1

Table 4.CDR 4 homolog proteins in fungi.

Eurotiomycetes			*Saccharomycetes*		*Sordariomycetes*	
CDR4	**Species**	**Homologs**	**Species**	**Homologs**	**Species**	**Homologs**
	Ajellomycescapsulatus	1	*Candida albicans*	1	*Fusariumoxysporum*	4
	Aspergillusterreus	4			*Fusariumverticillioides*	1
	Coccidioidesimmitis	1			*Magnaportheoryzae*	2
	Coccidioidesposadasii	4			*Neurosporacrassa*	1
					Neurosporatetrasperma	1

Studies on *Fusarium* species suggested that PDR and MRP subgroups harbor several genes in azole response and upregulate the transcriptional levels in *FgABC* homologs while deletion of *FgABC*3 and *FgABC*4 induce azole susceptibility and reduce virulence as compare to the wild type of Fusarium graminearium (Puri, *et al.,* 2009). Clinical isolates of *Candida albicans* revealed over expression CDR1 and CDR2 that encodes the two homolog genes of ATP binding family and the MDR gene that codes to the major facilitator family (Ernst, *et al.,*2008). Whereby the deletion of the MDR1 gene from the clinical isolate which was over expressing this gene decrease the resistance of Fluconazole. This concluded that MDR is directly involved in fluconazole resistance in the isolate (Puri, *et al.,* 2009). Thus the mechanism of ABC and MFS transporters in the fungal virulence is also involved on the base of the mutations and the upregulation of cis regulatory elements.

Molecular Mechanism of the conserved drug transporters in fungi

ATP binding cassettes comprised of transmembrane domains with highly conserved amino acid based proteins. They are the most widely spread proteins in prokaryotes and eukaryotes acting as transporters and receptors so, considered more crucial in cellular homeostasis. The molecular underlying mechanism ofaction for the PDR and MDR family domain is continued through the efficient coupling of ATPhydrolysis that leads to the drug transportation.

MDR studied by several mechanisms asrandom mutagenesis such as substrate specificity and inhibitors sensitivity as alanine mutagenesis of CDR1, TMS5 and TMS1 in candida spp. revealed the role of helix in substrates binding and ATPase coupling in drugtransportation (Banerjee, *et al.,* 2020). The nucleotide hydrolysis of ABC domain is a conserved basal mechanism of ATPase in fungi (Saini, *et al.,* 2005). Fungal NBDS(Nucleotide binding domain)are nonequivalent in functionality throughout thegenome. The main feature walker A-(GXXGXGKS) T and X represent any amino acid in the consensus sequence and walker B (ΦΦΦΦD, where Φ is any aliphatic group and a signature motif(LSGGQ) which are crucial for the Mg^{2+} co-ordination and ATP hydrolysis in the ABC transporter domain from bacteria to human. Walker A motif of NBD (NBD1 N- terminal) of Pdr5 has lysine residue substitution for the ATPase activity (Puri, *et al.,* 2009). In the N terminal side of H loop, histidine residue is missing and on the C terminal domain NBD2 the signature motif is disintegrated (Puri, *et al.,* 2009). According to the crystal structure of the bacteria the mechanism of the NBDS element represent the head to tail placement of NBDS to walker A with NBD1 and the signature motif NBD2 build ATP binding site. In this way Pdr 5 have one intact and an altered ATP binding side on another side. In replacement of Lys^{911} residue on the walker A motif of NBD2 yield sensitivity to the cells in the exposure of the known Pdr5 substrates. However, in contrast the replacement of Cys^{199} residue on the walker A motif of NBD1 does not induce drug resistance. In putative carboxylate (GLU^{1036}) the catalytic dyad His^{1068} (histidine) residue being investigated and an anticipated mutant E1036A could not hydrolyze ATP and revealed the cell drug sensitive. The replacement of alanine for his^{1068} does not act on the ATPase steady state, as it selectively reduce the R6G (Rhodamine6G) transport and leads the cells sensitive to azoles. This concludes the suggestion that the Kinetics of drug transporters and the hydrolysis of ATP are responsible for the substrate selection (Ernst, *et al.,* 2008). Moreover, the function of the transporters have been studied in many aspects as absorption and metabolism but the elaborative role of the transporters is still under study that require to cover their physiological role with normal and pathogenicity

Table 5. MDR homolog proteins in fungi.

MDR	*Eurotiomycetes*		*Saccharomycetes*		*Sordariomycetes*	
	Species	**Homologs**	**Species**	**Homologs**	**Species**	**Homologs**
	Aspergillus clavatus	**2**	***Candida albicans***	**36**	***Fusarium graminearum***	**1**
	Aspergillus Flavus	**2**	***Saccharomyces cerevisiae***	**3**	***Fusarium oxysporum***	**2**
	Aspergillus fumigatus	**8**			***Neurospora crassa***	**20**
	Coccidioides immitis	**13**				
	Neosartoryafischeri	**2**				

Table 6.MRP homolog proteins in fungi.

MRP	Species	Homologs	Species	Homologs	Species	Homologs	Species	Homologs
	Aspergillus asculeatus	**13**	***Candida albicans***	**34**	***Schizosaccharomycesjaponicus***	**24**	***Fusarium graminearum***	**17**
	Aspergillus carbonarius	**18**	***Candida glabrata***	**16**	***Schizosaccharomycesoctosporus***	**24**	***Fusarium oxysporum***	**14**
	Aspergillus clavatus	**16**	***Saccharomycescerevisiae***	**82**	***Schizosaccharomycespombe***	**27**	***Fusarium verticillioides***	**11**
	Aspergillus flavus	**21**					***Magnaporthe oryzae***	**18**
	Aspergillus fumigatus	**13**					***Neurospora crassa***	**83**
	Aspergillus nidulans	**17**						
	Aspergillus niger	**13**						
	Aspergillus oryzae	**11**						
	Aspergillus terreus	**12**						
	Neosartorya fischeri	**16**						

2. MATERIALS AND METHODS

In order to study the conserved domains of pleotropic transport protein family. We mainly focused on the well-known drug resistant group of CDRp, MDRp and MRPp familyamong fungi and found out the available homolog proteins in fungi. The conserved domains of the homolog transporter proteins family has been studied on the base of protein blast in Fungi data base from (fungidb.org) in major fourfungal groups, as Eurotiomycetes, Saccharomycetes, Schizosaccharomycetes and Sordariomycetes.

3. RESULTS AND DISCUSSIONS

Study has focused on the number of homolog and its orthologs proteins in other pathogenic fungi. It has been found out that, in eurotiomycetes CDR1 protein have 2 homologes in *Aspergillus fumigates* and *Aspergillusterreus* 22 homologs in *Candida albicans* while former two classes have one homolog in *Schizosaccharomyces japonicas* and one in *Schizosaccharomycesoctosporus*, one in *Fusarium* spp. plant pathogenic fungi and one in *Magnaportheoryzae*as mentioned in **(Table 1).**While CDR2 have 17 homolog

proteins in Saccharomycetes group in *Candida albicans* while one in *Schizosaccharomycetes*group as **(Table 2).** However, CDR3 have only one homolog in well-known candida spp. As **(Table 3).** In Saccharomycetes. CDR4 have one homolog in *Eurotiomycetes, Ajellomycescapsulateus* four in *aspergillus terreous*, and one in *Coccidioidesimmitis*, four in *Coccidioides posadas*. In S*accharomycetes*one in *Candida albicans*, while, in Sordariomycetes , plant pathogenic fungi four homolog in *Fusarium oxysporum*one in *Fusarium verticillioides*two homolog in *Magnaportheoryzae*and one in *Neurosporacrassa*and *Neurosporatetrasperma as shown in* **(Table 4).** Moreover, MDR the second sub group of transporter family have 2 homolog in *Aspergillus clavatus*2 while, 2, 8, 1,3 and 2 homolog proteins respectively in *Aspergillus flavus, Aspergillus fumigates, Coccidioidesimmitis* and *Neosartoryafischeri* with in *Euromycetes. Saccharomycetes* contains the highest number 36 homolog in *Candida albicans*while 3 in *Saccharomyces cerevisiae*species. In *Sordariomycetes*one homolog in *fusarium graminarium* 2 in *fusarium oxysporum* and 20 in *neurosporacrassa*as mentioned in (**Table 5).**Third transporter group MRP have highest number of homologs among four selected groups of fungi as *aspergillus asculeatus spp.* has 13, *aspergillus carbonarius* has 18 and *aspergillus clavatus* has 16 while *Aspergillus flavus, Aspergillus fumigates, Aspergillus nidulans , Aspergillus niger , Aspergillus oryzae, Aspergillus terreus* and *Neosartoryafischeria* have 16, 21, 13,17,13,12,11,12 and 16 homologs respectively in *eurotiomycetes*. In *Saccharomycetes* the human pathogenic fungi *Candida albicans*has 34 homologs while, *Candida glabrata* and *Saccharomyces cerevisiae* have 16 and 82 homologous respectively. Schizosaccharomycetes have 24 in *Schizosaccharomycesjaponicas* and *Schizosaccharomycesoctosporus* and 82 homologs in *Saccharomyces cereviae*. The fourth group Sordariomycetes have 17 homologs in wheat blight *Fusarium qraminearum* 14 in *Fusarium oxysporum* 11, 18 and 83 homologs in *Fusarium verticillioides*, *Magnaportheoryzae* and *Neurosporacrassa* likewise as **(Table 6).**

4. CONCLUSION

In this brief review we enlighten the drug transporter family subdivisions and its orthologs in various group of pathogenic fungi on the basis of the selection of major PDR protein, the mechanism of action as efflux pumps transporters and their conserved domain interactions. ABC Proteins are majorly involved in multiple physiological stresses, detoxification and the transport of the metabolic residues. The over expression of the ABC transporters is a major cause of counteraction of the antifungal drugs that leads to the MDR strains. The identification of the selective substrate and its interaction in various homologs proteins can be a strategy to understand the specificity of ABC transporters. This review provide the enormous information on the existence of drug transport proteins in various fungal groups as well as the future emergence of antifungal resistance. This review will help the researcher and physicians to look into the genetic basis of underlying mechanism of antifungal resistant proteins in various pathogenic fungi.

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