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Multi omics by LC-MS/MS to search small molecule ligands of nuclear receptors to control transcription of pharmaceutical active proteins for drug discovery

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Abstract

Multi Omics by LC-MS/MS is useful tool to search the ligands to control transcription of pharmaceutical active proteins such TNF, IL-1 and peroxisome.

How to search the small molecule ligands of the nuclear receptors to control transcription of pharmaceutical active properties using multi omics by LC-MS/MS

Osaka university shimadzu analytical innovation research laboratory is developing multi omics (MO) package on Garuda platform [1] that have statist analysis (principal components analysis (PCA)) and correlation analysis (principal components analysis (PCA)) and correlation analysis (the gene ontology analysis and pathway analysis) to treat LC-MS/MS data expressed in KEGG map in Figure 1. We believe that MO that is useful tool to discover a new drug as the interacted inhibitors of the small molecule ligands of nuclear receptor (NR) bound to promoter DNA to control transcription of pharmaceutical active proteins. NR has both L- domain binding to the small molecule ligands and D-domain binding to the promoter DNA as transcription factor. The human 48 NR contain 40 orphan receptors and 8 endocrine receptors that bind steroid hormones ligands produced from cholesterol by metabolism with CYP11, 17, 19 and 21 etc. Some ligands of orphan NR are unknown yet in Figure 2.

We have developed FK506 NF-AT transcription inhibitor [2], FK228 PPAR inhibitor [3], NF-kB Decoy oligo nucleotide (ON) [4,5]

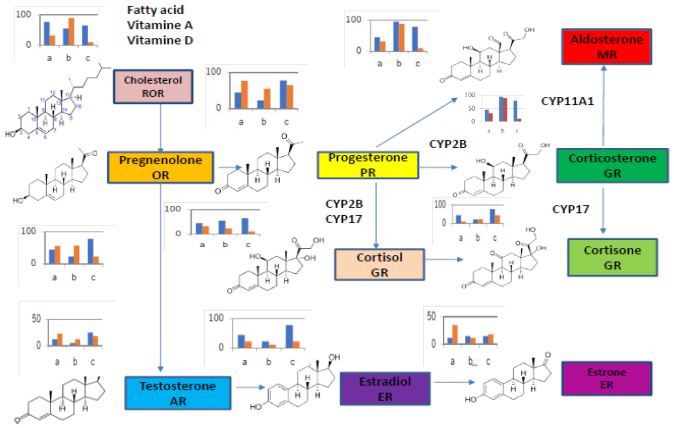

Figure 1. PCA Result of LC-MS/MS data expressed in KEGG map of steroid metabolism

Endocrine receptors		Adopted orphan receptors		Orphan receptors	
NR	Ligand	NR	Ligand	NR	Ligand
GR	Glucocorticoid	RXR	CYP 9-cis-retinoic acid	SHP	Unknown
MR	Mineralocorticoid	PPAR	CYP Fatty acids	DAX-1	Unknown
PR	Progesterone	LXR	CYP Oxysterol	TLX	Unknown
AR	Androgen	FXR	CYP Bile acids	PNR	Unknown
ER	Estrogen	PXR	CYP Xenobiotics	GCNF	Unknown
TR	Thyroid hormone	CAR	CYP Androstane	TR2,4	Unknown
RAR	Retinoic acid	HNF-4	CYP Fatty acids	NR4A	Unknown
VDR	Vitamin D (bile acid)	ROR	Cholesterol, retinoic acid	Rev-erb	Unknown
		ERR	Estrogen?	COUP-TFII	Unknown

Figure 2. Ligands and nuclear receptor as transcription factor

and AO85 Exon Skipping ON [6,7] that control transcription. FK506 and NF-κB decoy ON inhibits expression of inflammatory cytokines, such as TNF and IL-1 which trigger inflammation cascades to dermatitis. Antisense ON 18-mer 20-OMeRNA/ENA chimera (AO85) had the most potent activity for inducing exon 45 skipping of the dystrophin reading frame to allow production of an internally deleted dystrophin protein with functional benefit for DMD patients who have out-of-frame deletions. We presented plasma, urine, tissue MO and identified many transcription factors bound to a new promoter DNA of the platelet factor 4 [8] or a known promoter DNA of CYP3A4 by nanospray LC-MS/MS after in-gel tryptic digestion of spots SDS page electrophoresis. We will describe these unpublished studies as Articles in this journal continuously.

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Conflicts of interest

The authors declare no conflict of interest.

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