Development of a human PBMC TXG-MAPr as a mechanistic framework to interpret toxicodynamic variability across the human population

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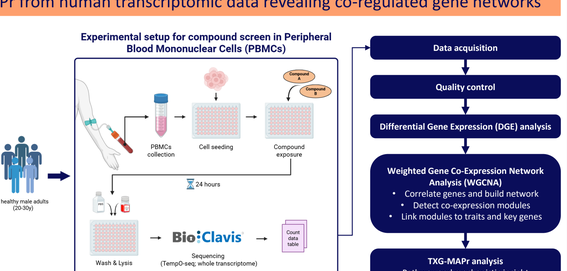
INTRODUCTION

Accurately capturing interindividual variability in human toxicodynamic responses is essential for reliable chemical safety assessment. While toxicokinetic variability is well characterized, our understanding of how individuals differ in their cellular responses to chemicals, particularly across stress and immune signaling pathways, remains limited. Freshly isolated peripheral blood mononuclear cells (PBMCs) offer a physiologically relevant human model to study coordinated pathway responses across donors. Network-based transcriptomic approaches, such as the PBMC TXG-MAPr, enable systematic mapping of compound-induced gene co-expression modules, providing a mechanistic framework to interpret interindividual variability and support the refinement of toxicodynamic uncertainty factors (UFs).

Generation of the PBMC TXG-MAPr from human transcriptomic data revealing co-regulated gene networks

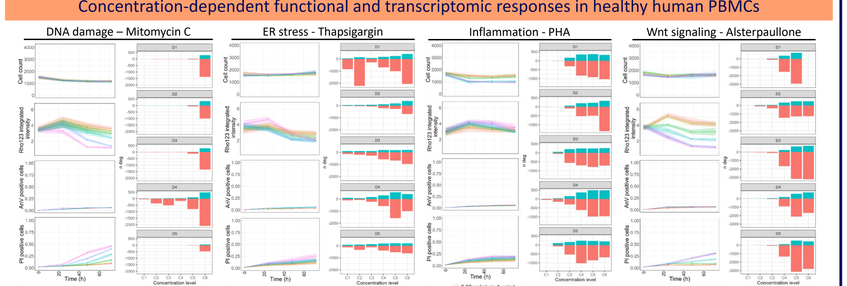
Cellular stress pathway	Compounds
ER stress	Tunicamycin
	Thapsigargin
Oxidative stress	CDDO-me
	Sulforaphane
	TBHQ
Inflammatory signaling	TNFα
	IL1β
	BMS345541
	LPS
	Imiquimod
	Fedratinib
	PMA
DNA damage	Cisplatin
	Mitomycin C
Mitotoxicity	Rotenone
	Antimycin A
	CCCP
T-cell agonist	PHA
Immunotoxicant	Cyclosporin A
Nuclear hormone receptors	Drospirenone
	GW4064
	Dexamethasone

Cellular stress pathway	Compounds
Metal & heat shock response	CdCl
	HgCl
Wnt signaling	Alsterpaullone
	Silmitasertib
Cytoskeleton	Colchicine
Calcium channel	Verapamil
Proliferation – survival signaling	Taselisib
	GSK690693
	PD032501
	SB202190
	Tandutinib
Transporter – ion channel	A425691
	Capsazepine
Mitosis	Alisertib
	SU9516
Stress kinase signaling	PH79804
Metabolism	Mevastatin
	Vidofludimus
GPCR receptors	Taranabant
AMPK pathway	Dorsomorphin
Autophagy	Rapamycin



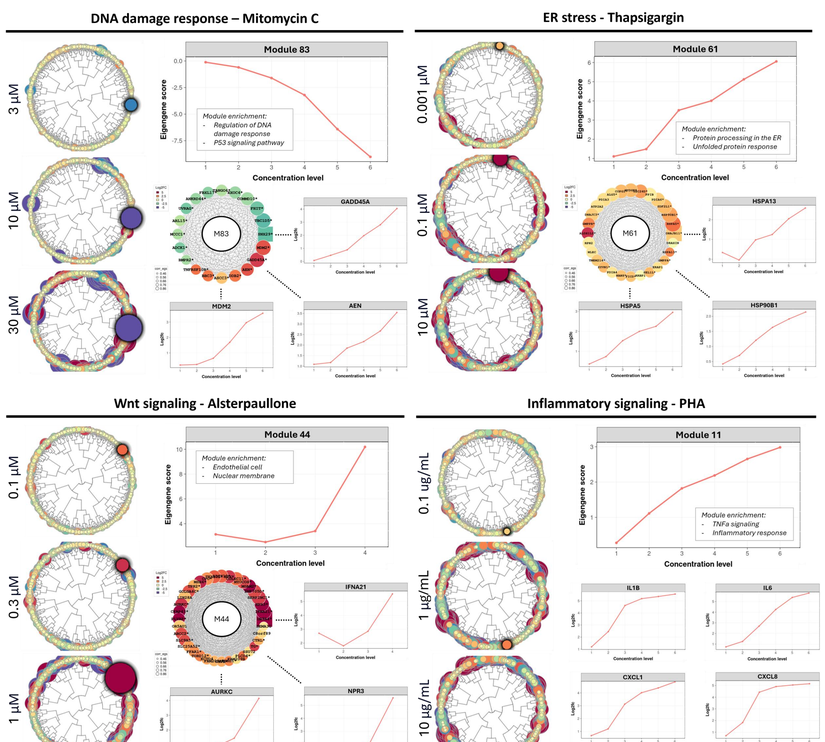
PBMCs from five donors were exposed to 43 mechanistically diverse compounds for 24 hours. Transcriptomic profiling using TempO-Seq (whole transcriptome) followed by differential expression analysis (DESeq2) and co-expression network analysis (WGCNA) generated the foundational data for the interactive TXG-MAPr, enabling exploration of coordinated pathway responses across donors and compounds.

Concentration-dependent functional and transcriptomic responses in healthy human PBMCs



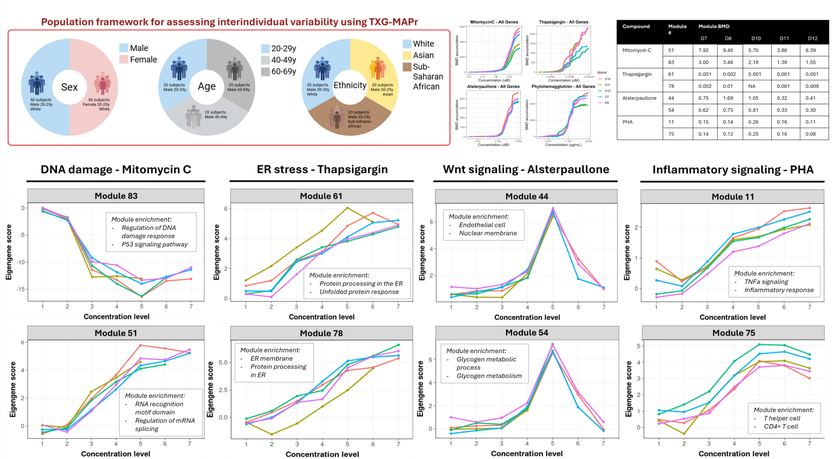
PBMC TXG-MAPr reveals pathway-specific gene co-expression modules

Each module represents a distinct group of closely co-regulated genes that tend to behave similarly across conditions. Activation indicates how these gene groups respond together in a coordinated manner to chemical exposure. This interactive map allows clear visualization and easy comparison of pathway responses across all donors.



Data from all 43 compounds were used to generate the TXG-MAPr; four representative compounds are highlighted here.

Compound-specific transcriptomic responses reveal interindividual variability across PBMC donors



Compound	Module #	Module BMD				
		D7	D8	D10	D11	D12
Mitomycin C	51	7.92	9.40	5.70	3.86	6.39
	83	3.00	3.46	2.16	1.39	1.55
Thapsigargin	61	0.001	0.002	0.001	0.001	0.001
	78	0.002	0.01	NA	0.001	0.009
Alsterpaullone	44	0.75	1.69	1.05	0.32	0.41
	54	0.62	0.73	0.81	0.33	0.30
PHA	11	0.15	0.14	0.26	0.16	0.11
	75	0.14	0.12	0.25	0.16	0.08

- Transcriptomic responses from five PBMC donors (male and female) were analyzed to evaluate donor-specific pathway activation
- TXG-MAPr module scores (or eigengene scores) reveal compound-specific activation patterns, highlighting variability in pathway responses between donors
- This framework will be used to quantify interindividual variability across larger population groups

CONCLUSION

- The PBMC TXG-MAPr organizes compound-induced gene expression into co-regulated modules, providing a mechanism-focused framework to compare pathway responses across donors and compounds and assess interindividual variability in stress response activation.
- This framework supports human-relevant chemical risk assessment by linking in vitro transcriptomic responses to pathway-level mechanisms and population variability.

FUTURE PERSPECTIVES

- Project whole-transcriptome data from ~200 donors onto the PBMC TXG-MAPr reference framework to systematically characterize interindividual variability in stress pathway activation across sex, age, and ethnic groups.
- Quantitatively assess donor-specific transcriptional responses to eight selected compounds across six concentrations, enabling identification of pathways and modules that vary in activation across the human population.

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