Supplementary Material

Transcriptional regulation of drug metabolizing CYP enzymes by proinflammatory Wnt5A signaling in human coronary artery endothelial cells

Tom Skaria^{1, 2}, Esther Bachli³, Gabriele Schoedon^{1*}

¹Inflammation Research Unit, Division of Internal Medicine, University Hospital Zürich, Zürich, Switzerland, ²School of Biotechnology, National Institute of Technology Calicut, Kerala, India, ³Department of Medicine, Uster Hospital, Uster, Switzerland.

*Correspondence

Gabriele Schoedon

Email: klinsog@usz.uzh.ch

Supplementary Methods

Supplementary Results

Supplementary Table 1. Genes regulated (≥ 2 fold up or down) by 4 h Wnt5A treatment in HCAEC. Data are from 3 independent array experiments.

Supplementary Table 2. Substrate compounds of CYP1A1 and CYP1B1 retrieved from cytochrome P450 database SuperCYP

(http://bioinformatics.charite.de/supercyp/index.php?site=home, accessed through 'CYP-drug interaction' on 03.08.2020), and SLCO2B1 substrates retrieved from metabolism and transport database Metrabase (http://www-metrabase.ch.cam.ac.uk/, accessed through 'search by protein' on 03.08.2020).

Supplementary Table 3. Genes regulated (≥ 2 fold up or down) by 4 h Wnt5A/IL-1 β combination treatment in HCAEC. Data are from 3 independent array experiments.

Supplementary Table 4. Regulated genes of drug and xenobiotic metabolism pathways significantly (P < 0.05) enriched in 4 h Wnt5A+IL-1 β transcriptome of HCAEC. Data are from 3 independent array experiments.

Supplementary Figure 1. Drug and xenobiotic metabolism pathways most significantly (P < 0.05) regulated by 4 h IL-1 β treatment in HCAEC. Pathways represented as histograms are ranked by the –log value (P value). This figure is generated by reanalysing data published in *Skaria, T., Bachli, E., and Schoedon, G. (2019). Gene Ontology Analysis for Drug Targets of the Whole Genome Transcriptome of Human Vascular Endothelial Cells in Response to Proinflammatory IL-1. Frontiers in Pharmacology 10.* The purpose of reanalysing data from above-said study was to identify the myocardial drug and xenobiotic metabolism pathways regulated by 4 h IL-1 β treatment (which was not contained in previous study) that served as an additional positive control for comparing the effects of Wnt5A/ IL-1 β combination treatment with sole Wnt5A treatment in HCAEC.

Supplementary Methods

Primary cell culture

HCAEC (Cat. No. CC-2585, Clonetics, Lonza) were cultured in EGM-2MV Single Quots and 5% FBS (Clonetics, Lonza)-enriched EBM-2 medium (Clonetics, Lonza) in a Class 100 HEPA air filtered SteriCult system (Fisher Scientific, Switzerland) as described (Skaria et al., 2017; Skaria et al., 2019). HCAEC used in the present study were tested positively and functionally for CD31 (PECAM-1), CD105 (endoglin), von Willebrand Factor VIII, and acetylated low-density lipoprotein uptake as confirmed by the manufacturer (Lonza, Cell Systems). Masked low-level contamination in cultures were prevented by using antibiotic-free culture medium during the entire study period. Experiments were carried out using HCAEC from passages 3-6 only. HCAEC monolayers were treated with vehicle (sterile pyrogen free 0.1% human serum albumin in 0.9% NaCl) and recombinant human/mouse Wnt5A (250 ng/mL, Cat. No. 645-WN, R&D systems) alone or combined with recombinant human IL-1 β (20 U/mL, Cat. No. 200-01B, PeproTech) for 4 h. All pipetting steps were carried out using Biopure ep Dualfilter T.I.P.S. sterile filter tips (Eppendorf) or TipOne aerosol barrier sterile filter pipet tips (USA Scientific).

Whole genome expression profiling and gene ontology analysis

Differential gene expression analysis by competitive two-colour hybridization of cRNA probes onto 4×44K Human Whole Genome Oligonucleotide microarrays (Agilent Technologies) was conducted as described (Skaria et al., 2017; Skaria et al., 2019). Following isolation of total RNA using RNeasy Mini Kit (Qiagen, Basel, Switzerland), RNA was quantified by Nanodrop spectrophotometry. RNA integrity was measured with the Agilent 2100 Bioanalyzer System (Agilent Tech., Basel, Switzerland). Only RNA samples with a RNA integrity number (RIN) >9 were used for the microarray experiments. From each of treated samples, 500 ng of total RNA were subjected to reverse transcription and labelling with Cy3- and Cy5-CTP employing the two-colour Quick Amp Labelling Kit (Agilent Tech., Switzerland) comprising internal control probes and spike in's (labelled Spike A mix with Cy-3 and Spike B mix with Cy-5) to control reaction performance and background normalization of arrays. cRNA fragmentation and hybridization onto the Human GE 4×44K V2 Microarray chips were conducted in accordance with the Quick Amp Labelling protocol (Agilent Techno., version 5.7, 2008). Ozone-induced deterioration of cyanine dyes were avoided by washing then array chips with stabilization and drying solution (Agilent Tech., Switzerland). Scanning, feature extraction and pre-processing in conjunction with data normalization of the microarrays were conducted using the Microarray Scanner and Feature Extraction Software 10.7 (Agilent Tech. Inc.) employing default settings for Agilent 4×44 K two-colour arrays. Spot value normalization was performed with the default linear-lowess normalization. Log ratios and P value Log ratios, calculated based on extensive error model and pixel level statistics computed from the feature and background for each spot, were used to indicate significant differential regulation of genes of the whole transcriptome after linear-lowess normalization and provided in all microarray datasets deposited in NCBI GEO database (available with accession numbers GSE145987, GSE62281 and GSE146691).

The accession GSE145987, presented for the first time in this manuscript, contains 2 independent microarray experiments of HCAEC treated with Wnt5A for 4 h (2 independent replicates). The accession GSE146691, presented for the first time in this manuscript, contains 3 independent microarray experiments of HCAEC treated with Wnt5A/IL-1 combination for 4 h. The accession GSE62281 contains the third independent microarray data of HCAEC treated with Wnt5A for 4 h (third independent replicate). Of these three accession numbers, only the accession GSE62281 is associated with a previous publication (Skaria et al., 2017). However,

the aforesaid previous research article (Skaria et al., 2017) contained analysis/description of the microarray data set of only 8 h Wnt5A alone and 8 h IL-1 alone treatment of HCAEC along with several other experiments addressing the effects of chronic Wnt5A treatment on endothelial barrier function pathway. It has to be noted that though microarray data of single 4 h Wnt5A treatment experiment has been contained in the GSE62281, the aforesaid previous publication (Skaria et al., 2017) contained neither analysis nor description of the 4 h Wnt5A alone or combined Wnt5A/IL-1 microarray data. Furthermore, the aforesaid previous study (Skaria et al., 2017) did not involve any gene ontology analysis for the direct drug/ drug metabolising targets even for the 8 h Wnt5A- or 8 h combined Wnt5A/IL-1-treated whole genome transcriptome of HCAEC.

To identify genes that were consistently regulated ≥ 2 -fold in their expression in three independent microarray experiments in each treatment group, the pre-processed microarray data (that underwent linear-lowess normalization and error estimates) were further analysed using GeneSpring GX 9.0 Software (Agilent Tech. Inc.) with default settings for two-colour arrays. Genes regulated ≥ 2 -fold in their expression as found from the second line GeneSpring analysis (Supplementary Tables S1 and S3) were subjected to gene ontology analysis of drug and xenobiotic metabolising enzymes using Metacore GeneGO software version 6.32.69020 (Thomson Reuters, http://portal.genego.com) after setting a P value < 0.05 and FDR cut off (0.05).

References

- Skaria, T., Bachli, E., and Schoedon, G. (2017). Wnt5A/Ryk signaling critically affects barrier function in human vascular endothelial cells. *Cell Adh Migr* 11, 24-38.
- Skaria, T., Bachli, E., and Schoedon, G. (2019). Gene Ontology Analysis for Drug Targets of the Whole Genome Transcriptome of Human Vascular Endothelial Cells in Response to Proinflammatory IL-1. *Frontiers in Pharmacology* 10.

Supplementary Results

Upregulated genes	Downregulated genes
ALDH1L1	A2ML1
ATAD3C	ААТК
C1orf172	ABCB5
C2CD4A	ACOT6
C6	ACSM5
CBLN4	AIM2
CEACAM21	ALS2CR12
	ALSZCK 12 ANKRD30B
CELA3A	
CLCA2	APOL6
CNTN2	ATXN3L
CYP1A1	BCL11A
CYP1B1	BCOR
DDO	BEST1
DNM1L	BHMT
DSCR6	BIN2
EDNRA	C10orf71
EFCAB9	C10orf81
ELK1	C12orf40
ETV3	C12orf54
FAM90A7	C12orf61
FLJ10038	C14orf23
FLJ39080	C14orf86
GSG1	C18orf34
GYPE	C1orf130
HEATR1	C1orf141
HOMER1	C1orf192
HYALP1	C1orf227
IL22RA2	
	C20orf71
ITGA4	C2orf72
KCNS2	C5orf60
KCTD12	C6orf112
KIR3DL3	C7orf66
KRT24	C7orf72
LOC100130428	C9orf66
LOC100131702	CAGE1
LOC100507699	CCL28
LOC283588	CCNC
LOC440386	CD200R1
MAGEC2	CDH23
MIXL1	CEACAM3
MS4A2	CHI3L1
MYL10	CHRM3
MYO3A	CHRNA4
MYOD1	CLDN19
NEUROD2	CLEC4M
OR6Y1	CLRN2
OR8J1	CMAHP
PADI6	CNKSR2
PGC	CSMD2
POU5F2	CTAGE5
PO05F2 PSG5	DAPL1
PTAR1	DCHS2
PTCD3	DCLK1
PTPRC	DEFB113
RNASE6	DKFZp547J222
ROBO2	DMGDH
S100A14	DNAH17
SCARNA23	DTHD1
SGCD	EDNRB

Supplementary Table 1. Genes regulated (≥2 fold up or down) by 4 h Wnt5A treatment in HCAEC. Data are from 3 independent array experiments.

SHANK2	EIF3E
SHISA2	ENO4
SLA	EPAG
SLC10A7	EPO
SLC16A2	F13A1
SLC24A4	FABP12
SLC39A12	FAM163A
SLC4A5	FBP2
	FGF16
SLCO2B1	
TBX21	FHAD1
TDRD6	FLJ46120
TLE1	FMN2
TMEM31	FRY
TTC30A	FSTL4
UMODL1	GAFA1
VIT	GATA4
ZNF780A	GCNT3
ZRANB3	GCNT7
	GFAP
	GFRAL
	GNAO1
	GPR6
	GPR77
	GRIP2
	GUCY2C
	HIST1H2BA
	HMCN2
	HNF4A
	HOXD9
	HPGD
	HPSE2
	HSPB7
	IGF2
	IKZF1
	IL16
	IL2
	IL31
	ISL2
	ITGAD
	ITGB6
	KAZN
	KCNV1
	KIAA1875
	KLHL15
	KLK12
	KRTAP19-4
	KRTAP7-1
	LAIR2
	LILRB4
	LIPC
	LOC100128077
	LOC100128164
	LOC100128356
	LOC100128338
	LOC100129072
	LOC100129119
	LOC100129413
	LOC100130157
	LOC100130255
	LOC100130452
	LOC100130701
	LOC100130849
	LOC100131581
	LOC100132147
	LOC100132738
	LOC100132738
	LOC100144597 LOC100289333

LOC100291323
LOC100507634
LOC128322
LOC150568
LOC150935
LOC220980
LOC285370
LOC285778
LOC286190
LOC339862
LOC401433
LOC440117
LOC442028
LOC494558
LOC554201
LOC645591
LOC646034
LOC728084
LOC728192
LOC729177
LOC729444
LOC90834
LOC91149
LPHN3
LRRTM2
MAGEB5
MCHR2
MCTP2
MFSD6L
MGC12916
MNDA MUC12
MUC12
MYBL1
MYOCD
NCRNA00264
NCRNA00284
NCRNA00307
NDUFS7
NEB
NHLH1
NPIPL3
NT5DC4
NTNG1
ODF2L
OPN5
OR4C16
OR4D2
OR4F4
OR6C76
OR9G4
PABPC1P2
PIAS4
PLB1
PLCH1
PLP1
POM121L1P
POPDC2
PPP1R1C
PRAMEF13
PROZ
PRPS1
PSG9
RAD9B
RGR
RUNX2
SAMD12
SAMD 12 SASH1

SCNN1A
SEC14L3
SEMG2
SERPINI2
SFTPB
SHCBP1L
SLC14A1
SLC3A1
SNAR-C3
SNORA2B
SNORA77
SPANXB2
SPINT4
SST
ST8SIA6
STAP1
SULT1C2
SYCP2L
SYT6
TARP
TCEB3C
TCTN3
TDRD5
TFAP2D
THUMPD2
TIMP1
TPTE2
TRAF3IP3
TRAPPC10
TRIOBP
TRPM6
TTTY21
TTTY3
TTTY8
TUBBP5
TXNRD3NB
UBASH3A
UBE2D3
UBE4B
UGT1A4
UGT1A6
USH2A
WIPF3
ZBP1
ZCCHC11
ZNF167
ZNF354C
ZNF853
ZNF883
ZSCAN5B

Supplementary Table 2. Substrate compounds of CYP1A1 and CYP1B1 retrieved from cytochrome P450 database SuperCYP

(http://bioinformatics.charite.de/supercyp/index.php?site=home, accessed through 'CYP-drug interaction' on 03.08.2020), and SLCO2B1 substrates retrieved from metabolism and transport database Metrabase (http://www-metrabase.ch.cam.ac.uk/, accessed through 'search by protein' on 03.08.2020).

Enzyme/	CYP1A1	CYP1B1	SLCO2B1
transporter Substrates	Acriflavinium-chloride	Amodiaquino	Dipoprostopo
Substrates	Alum	Amodiaquine Caffeine	Dinoprostone Penicillin G
	Amiodarone		Bromosulfophthalein disodium
	Amodiaquine	Dibutylphthalate Docetaxel	Estrone-3-sulfate
	Benzydamine	Erythromycin Estradiol	Dehydroepiandrosterone sulfate Taurocholic acid
	Capsaicin		Pravastatin
	Chloroquine	Estrone Flutamide	
	Cinnarizine		Glyburide
		Hydrogen-	Pregnenolone sulfate Aliskiren
	Dacarbazine	peroxide Melatonin	Pemetrexed
	Daunorubicin		Fluvastatin
	Debrisoquine Decamethrin	Oxaliplatin Procarbazine	Bosentan
	Diclofenac		
		Progesterone	Etoposide
	Dronabinol	Retinol (vit A)	Methanone, [4-[4-(3,4-dihydro-6,7-
	Erythromycin Estradiol	Rosuvastatin Testosterone	dimethoxy-2(1H)-isoquinolinyl)-6,7-
			dimethoxy-2-quinazolinyl]hexahydro-1H-1,4-
	Estrone	Theophylline	diazepin-1-yl](3,4-dihydroxy-1-pyrrolidinyl)
	Etacrynic acid		Rocuronium N-methyl-guinidine
	Ethinylestradiol Flunarizine		
			Digoxin Pitavastatin
	Flutamide		
	Fluvastatin		Atorvastatin
	Granisetron		Telmisartan
	Haloperidol		Rosuvastatin
	Ipriflavone		CP 671305
	Levothyroxine- sodium		M17055
	Melatonin		Telmisartan glucuronide
	Menadione		Levothyroxine Talinolol
	Mercaptopurine		
	Nicotine		Tebipenem pivoxil
	Nitrofurantoin		BDE 47 BDE99
	Omeprazole		BDE153
	Oxaliplatin		
	Paracetamol		Bromosulfophthalein
	Perazine		Latanoprost acid Salozinal
	Phenacetin		
	Prazosin Procarbazine		3-Pyridinecarboxylic acid, 6-[[(2S)-3-
			cyclopentyl-1-oxo-2-[4-(trifluoromethyl)-1H-
	Progesterone		imidazol-1-yl]propyl]amino]-
	Raltegravir		Ethinylestradiol-3-O-sulfate
	Retigabine Biboflovin (vit B2)		Cerivastatin
	Riboflavin (vit B2)		Montelukast
	Riluzole		Sulfasalazine
	Tamoxifen		Fexofenadine
	Testosterone		Eltrombopag (betaR,deltaR)-5-cyclopropyl-2-
	Theophylline		
	Toremifene		(4fluorophenyl)-4-[[[(3
	Troglitazone		fluorophenyl)methyl]amino]carbonyl]-
	Zotepine		beta,delta-dihydroxy-1H-imidazole-1-
			heptanoic acid
			Unoprostone carboxylate
			Ezetimibe glucuronide
			Iloprost
			Thromboxane B2

	Scutellarein 6-O-beta-D-glucuronide
	Scutellarein 7-O-beta-D-glucuronide

Upregulated genes	Downregulated genes
ABTB2	A2ML1
ADIM21	ACOT6
ADAMTS9	ACSM5
AGMO	ADRB1
AMOT	AGBL2
AMPD3	AJAP1
APOBEC3G	AKNA
APOL2	ALDOAP2
APOL3	ANK3
APOL4	ANKRD20A2
APOL6	ANKRD20A9P
ARHGAP9	ANKRD23
ARID5B	ANKRD5
ATF3	ANXA11
ATP2C2	AQP9
ATPBD4	ARHGAP18
BARHL1	ARHGEF4
BATF3	BCL11A
BCL2A1	BEST1
BCL6	BIN2
BDKRB2	C10orf99
BHLHE41	C12orf54
BICC1	C13orf15
BIRC3	C14orf23
BMP2	C18orf34
C10orf93	C1orf141
C11orf40	C1orf229
C11orf96	C5orf52
C12orf50	C5orf62
C12orf53	C7orf58
C14orf28	C9orf66
C15orf48	CACNA1G
C19orf29OS	CAGE1
C1orf172	CCDC108
C1QTNF1	CCDC121
C1R	CCDC165
C1S	CCDC48
C22orf33	CCNC
C2CD4A	CDC14B
C2CD4B	CDCA7L
C3	CEACAM7
C3orf52	CES1P1
C6	CH25H
C6orf58	CLEC4GP1
C7orf51	CMAHP
C8orf4	CNIH3
C8orf80	COL22A1
CACNA1B	COX7B2
CAMTA1	CSMD2
CAMITAT CBLN4	CXorf22
CBR3	CXorf51
CBR3 CCL1	CYP26B1
CCL17	DCHS2
CCL2	DDIT4L
CCL2 CCL20	DEFB113
	-
CCL3	
CCL3L3	DNAJB4
CCL4	DNALI1
CCL5	DPP6
CCL7	DSPP
CCL8	E2F2

Supplementary Table 3. Genes regulated (≥ 2 fold up or down) by 4 h Wnt5A/IL-1 β combination treatment in HCAEC. Data are from 3 independent array experiments.

CCRN4L E2F8 CD69 EBF1 CD7 EFCAB11 CD70 EFDA3 CD83 ENAH CFB ENAH CFB EPHA5 CHOH EPN3 CHR2 EVI2B CHRNA2 FAM201A CHRNA2 FAM201A CHTD4 FOFEP3 CLCC4A FULP1 CLC44 FULP2 CNTA FL25328 COL2741 FL41484 CPEB4 FRY CSF1 GFOD1 CSF2 GMAP7 CSF3 GJA4 CSF3 GJA4 CXC11 GPC6 CXC13 HOX87 CXC14 GPC6 CXC15 HRC11 CXC16 HS3511 CXC17 HS6513 CYP10 HTHB DV711 HS76 CXC12 HA763 CYL10 HTR10 CYC11		
CD7 EFCAB11 CD70 EH03 CD83 EH73E CD84 ENAH CFB EPHA5 CHDH EPN3 CHP2 EV/28 CHRD2 FAM124B CHRNA2 FAM124B CHRNA2 FAM22D CHRNA2 FAM22D CHTTP EV/28 CHTTP FAM24D CHTTP FAM24D CHTTP FAM24D CHTTP FAM24D CHTTP FAM24D CLEC2D FGFB73 CLEC4A FLUP1 CD1741 FL/25328 CD12741 FL/25328 CSF1 GATA4 CSF2 GMAP7 CSF3 GLA4 CSRP2 GLA4 <td>CCRN4L</td> <td>E2F8</td>	CCRN4L	E2F8
CD70 EHD3 CD83 EF3E CDHR3 ENAH CPB EPN45 CHDH EPN3 CHD2 EV2B CHR02 FAM201A CHR02 FAM201A CHR02 FAM201A CHR02 FAM201A CHR02 FAM201A CHR03 FG512 CLD14 FG512 CLD14 FG512 CLC24 FAM248 CLC24 FLL2528 CNT14 FL2528 COL27A1 FLL41484 CPEB4 FRY CSF1 GF0D1 CSF2 GMAP7 CSF3 GJA4 CXC11 GPC6 CXC11 GPC6 CXC11 GPC6 CXC13 HAR51 CYP15 HC71 CXC16 HS3ST1 CXC17 HS6ST3 CYU10 HTR10 CYP141 HYD1 CYP151 </td <td>CD69</td> <td>EBF1</td>	CD69	EBF1
CD70 EH03 CD83 EFSE CDHP3 ENAH CFB EPN45 CHDH EPN3 CHD2 EVXB CHRNA2 FAM201A CHEC2 FGF12 CLD14 FGF12 CLC4A FLLP1 CNTA FL2528 COL27A1 FL141484 CPEB4 FRY CSF1 GROD1 CSF2 GIMAP7 CSF3 GJA4 CXC11 GPC6 CXC11 GPC6 CXC12 HAFB3 CXC13 HOX87 CYL1 GPC6 CXC14 GPC6 CXC15 HRC11 CXC16 HS3ST1 CXC17 HS6F3 GY	CD7	EFCAB11
CD883 EIF3E CDHR3 ENAH CFB EPHA5 CHDH EPH3 CHP2 EVI2B CHRDL2 FAM124B CHRNA2 FAM201A CHRNA2 FAM24D CHRNA2 FAM24D CHRNA2 FAM24A CHTED4 FAM74A1 CLDM1 FGFB73 CLEC2D FGFR2 CLEC4A FLLP1 CDNTA FL2S328 CONTA FL2S328 COL27A1 FL44484 CPEB4 FRY CSF1 GATA4 CSF2 GMAP7 CSF3 GATA4 CSR2 GATA4 CSR2 GATA4 CSR2 GNAP7 CSF3 GATA4 CSR2 GNAP7 CSR2 GATA4 CXCL10 GPC6 CXCL11 GNC2 CXCL2 HAP53 CXCL3 HAC71 <td< td=""><td></td><td></td></td<>		
CDHR3 ENAH CFB EPN3 CHDH EPN3 CHRD2 EV2B CHRN22 FAM201A CHRN22 FAM201A CHRN2 FAM201A CHRN42 FAM201A CHRN42 FAM201A CHRN42 FAM201A CHRN42 FAM201A CHR14 FGF12 CLD111 FGF12 CLD114 FGF12 CLC2A FGR93 CLC2A FGR93 CLC2A FLJ41484 CPEB4 FL2 CSF1 GF001 CSF2 GMAP7 CSF3 GJA4 CSR2 GKN2 CXCL1 GPC6 CXCL1 GPC6 CXCL3 HAF83 CYUD HTR10 CYP131 ICAF6 CYP141 HVN CYP151 ICAF6 CYP161 ICAF1 CXCL5 HRC11 <td< td=""><td></td><td></td></td<>		
CFB EPHA5 CHDH EPHA5 CHPD EVI28 CHRDL2 FAM124B CHRNA2 FAM22D CHRNA2 FAM22D CHRDL2 FAM124B CHRNA2 FAM22D CHTA FAM22D CIEC4 FAM74A1 CLDN14 FGFBP3 CLEC4A FILP1 CNTM2 FL25228 COLT7/1 FL41484 CNTA2 FL25282 COLT7/1 GATA4 CSF1 GF0D1 CSF2 GIMAP7 CSF3 GJA4 CSF2 GIMAP7 CSF3 GJA4 CXCL1 GNC2 CXCL1 GVGGA7B CXCL2 H2AFB3 CXCL2 H2AFB3 CXCL5 HRCT1 CXCL6 H3ST1 CXCL6 H3ST3 CYP1B1 ICA1L CYP1A1 ISF6 CYP1A1 ISF6 <tr< td=""><td></td><td>-</td></tr<>		-
CHDH EPN3 CHP2 EV/2B CHRDL2 FAM124B CHRNA2 FAM201A CHRNA2 FAM201A CHST6 FAM201A CITED4 FGFB73 CLDN1 FGFB73 CLEC2D FGFB73 CLEC2A FLJ25328 COL27A1 FLJ41484 CPEB4 FRY CSF1 GFD1 CSF2 GIMAP7 CSF3 GJA4 CSF1 GOLGA7B CX211 GOLGA7B CX212 HAF83 CX211 GOLGA7B CX212 HAF83 CX213 HOXB7 CX214 GPC6 CX215 HRCT1 CX216 HSST1 CYP1A1 HYP1N		
CHP2 EV/28 CHRDu2 FAM124B CHRNu2 FAM201A CHST6 FAM28D CIED4 FAM74A1 CLDM1 FGF12 CLEC4 FILP1 CLEC4A FILP1 CNTV2 FL25328 COL77A1 FL35328 COL77A1 FL414484 CSF1 GFOD1 CSF2 GIMAP7 CSF3 GJA4 CSF2 GIMAP7 CSF3 GJA4 CSF2 GIMAP7 CX3CL1 GNG2 CX3CL1 GNG4 CX41 GPE4 CX41 GNG4 CX3L1 GNG4 CX41 GNS50 CY41		-
CHRID2 FAM124B CHRNA2 FAM201A CHRNA2 FAM201A CHST6 FAM201A CITED4 FAM201A CLDM1 FGF12 CLDM4 FGF873 CLEC2D FGF873 CLEC2D FGF873 CNOT4 FL025328 CNTA2 FL255328 COL27A1 FL141484 CPEB4 FRY CSF2 GIMAP7 CSF3 GJA4 CSF2 GIMAP7 CSF3 GJA4 CSF2 GIMAP7 CSR2 GMAP7 CSR2 GMAP7 CSR2 GMAP7 CSR2 GMAP7 CSR2 GMAP7 CSR2 GMAP7 CX3L1 GOLGA7B CXC10 GPR116 CXC11 GPC6 CXC12 HAF83 CXC14 HOSB7 CXC15 HRC11 CXC16 H3SS11	CHDH	EPN3
CHRNA2 FAM201A CHST6 FAM25D CITED4 FAM25D CLDM1 FGF12 CLDM14 FGF12 CLDM14 FGF12 CLEC4A FILIP1 CLEC4A FILIP1 CNTM2 FL25328 COL27A1 FL41484 CRPE84 FRY CRIP1 GATA4 CSF1 GFOD1 CSF2 GIMAP7 CSF3 GJA4 CSR2 GIMAP7 CXCL1 GPC6 CXCL1 GPC6 CXCL1 GPC6 CXCL1 GPC6 CXCL3 HOXB7 CXCL5 HRC71 CXC16 HSST3 CYL0 HTR1D CYP1A1 HSST3 CYP1A1 HSST3 CYP1A1 IL16 DVAID2 KIA4239 DXAB LC101028402 DXAB LC2100128413 DIAB LC2100128413 <td>CHP2</td> <td>EVI2B</td>	CHP2	EVI2B
CHRNA2 FAM2D1A CHST6 FAM2BD CHST6 FAM2BD CITED4 FAM2AD CLDM1 FGF12 CLDM14 FGF12 CLDM14 FGF12 CLEC4A FILIP1 CLEC4A FILP1 CNTM2 FL25328 COL27A1 FL41484 CRPE84 FRY CRP11 GATA4 CSF1 GFOD1 CSF2 GIMAP7 CSF2 GIMAP7 CXC11 GUG2A CXC11 GUG37B CXC11 GUG37B CXC11 GPC6 CXC11 GPC6 CXC12 H2AF83 CXC13 H0XB7 CXC14 H2AF83 CXC15 HRC71 CXC16 H3ST11 CYPIA H2AF83 CYPIA H2AF83 CYPIA H2AF83 CYPIA H2AF83 CYPIA H2AF83 <	CHRDL2	FAM124B
CHST6 FAM26D CTED4 FAM74A1 CLDM1 FGF12 CLDM4 FGF873 CLEC2D FGF872 CLEC4A FILP1 CN0T4 FLG2 CNT2 FLJ55328 COL27A1 FLJ41484 CPEB4 GATA4 CSF1 GF0D1 CSF2 GMAP7 CSF3 GJA4 CSF2 GMAP7 CSF3 GJA4 CSF2 GKN2 CTHRC1 GIPR112 CSS1 GNC2 CXCL1 GOLGA7B CXCL1 GDCA7B CXCL3 HAFB3 CXCL4 HAFB3 CXCL5 HRCT1 CXCL6 HSST1 CXCR7 HS6ST3 CYP1A1 HYDIN CYP1A1 HYDIN CYP1A1 HYDIN CYP1A1 HYDIN CYP1A1 HYDIN CYP1A1 HYDIN	-	
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ENKUR LOC282980 ERC2 LOC284080 ERO1LB LOC285954 ETV3 LOC286068		
ERC2 LOC284080 ERO1LB LOC285954 ETV3 LOC286068	-	
ERO1LB LOC285954 ETV3 LOC286068		
ETV3 LOC286068		
ETV7 LOC286071		
F3 LOC286367	F3	LOC286367

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FER1L6-AS1	LOC91149
FGF18	LRRTM2
FGL1	LYPD1
FILIP1L	MAP7
FLJ25363	MBP
FLJ31104	MCF2L
FOXF1	MCHR2
FOXJ1	MDFI
FSTL3	MEF2C
G0S2	MNDA
GBP1	MTUS1
GBP3	MUC12
GBP4	MYCN
GBP5	NCRNA00284
GCH1	NCRNA00320
GFPT2	NEB
GK	NFIB
GOT1L1	NPIPL3
GPR37L1	NTNG1
GPR68	ODF2L
	-
GRAMD3	OR2K2
GRK1	OR2T12
GRM4	OR5L1
HAS3	OR9G4
HBS1L	OTX1
HCG4B	OVOS2
HERC6	PALMD
HEY1	PAQR4
HGF	PARP15
HIVEP2	PCDH11X
HLA-B	PCDH15
HLA-C	PLAC8
HLA-F	PLB1
HOMER1	PLEKHG4B
ICAM1	PPFIBP2
ICAM4	PRB4
ICAM5	PRICKLE1
ICOSLG	PRO0611
ID01	PRO1596
IER3	PRO1768
IFI30	PRODH
IFIH1	PRPS1
IFIT5	RASGRP3
IFNGR1	RASSF5
IFNGR2	RASSF9
IL10RA	RD3
IL15	RESP18
IL15RA	RFX4
IL18R1	RIN1
IL18RAP	SAMD13
IL1A	SEC14L3
IL1B	SEMG2
IL22RA2	SERTAD4
IL27	SFTPB
IL36G	SGCD
IL6	SGK223
IL8	SH3BP4
INHBA	SH3TC2

IQCA1	SHE
IRAK2	SIRPD
IRF1	SKOR1
IRX2	SLC22A2
ISG20	SLC4A10
ITGA1	SMAD6
ITGA4	SNAP91
JAM2	SNTG1
KCNE4	SOX18
KCNN2	SPANXN3
KDM6B	SPIC
KIAA0247	SRRM3
KIAA1644	ST8SIA4
KIRREL2	ST8SIA6
KLF6	SULT1C2
KLK3	SYNPO2
KRT24	TBX1
KRTAP3-2	TEX15
KYNU	THBD
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MAP3K8	
MCM9	
MDGA1	
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MMP1	
MMP10	
MRGPRX3	
MS4A2	
MSX1	
MTHFD2L	
MTMR7	
MUC4	
MYB	
MYOM1	
N4BP2L1	
NAB1	
NAMPT	
	1
NCOA7	
NEURL3	

NFKB1 NFKB1 NFKB10 NFKB12 NIN14 NIPAL4 NKA2 NKD2 NKD2 NKD2 NKX3-1 NMMT NOD2 NF7X1 NF6A1 NR6A1 NPE10 OR111 OR501 OR501 OR501 OR501 OR501 OR501 PDE1 POC PARP14 PDE5A PDC0		
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NFKBID NFKBIZ NIPAL4 NIPAL4 NIPAL4 NKAD1 NKD2 NKX3-1 NMMT NOD2 NK71 NPFX1 NR6A1 NUP2CL NUP1 OR1FI OR5011 OR512 OXIR PARD3 PARD4 PDE4D1P PDE5A PDFR PDFR PDFR PDFR PDFR <td></td> <td></td>		
NFK8IZ NINJ1 NINJ1 NIKAIN1 NKAIN1 NKAIN1 NKAIN1 NKX31 NKX3 NKX3 NKX3 NKX3 NMT NMT NMT NMT NR43 NR841 NR843 NR841 NUP62CL NUP1 OR10H1 OR11H1 OR11H1 OR411 OR5012 OXTR P2RY6 PARP14 PDESA POSGN2 OXTR P2RY6 PARP14 PDESA PDESA PDESA PDFR PDIM4 PDPR PDLM4 PDPR PDIM4 PDF PITNC1 PITRY2 PLC54 POUSF2 PRAS PRINS <td></td> <td></td>		
NINJ1 NIPAL4 NKAN1 NKAD2 NKXD2 NKX3-1 NMMT NOD2 NFTA1 NFA3 NR6A1 NUP22CL NUP10 OR50/1 OSE/R2 P		
NIFAL4 NKAIN1 NKAIN1 NKX2 NKX3.1 NMMT NOD2 NPT NRA3 NPG2L NUA2 NUA2 NUA3 NPG2L NRA3 NRA3 NRA3 NRA3 NRA4 PDESA POSGRA PDESA		
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NKX3-1 NNMT NOD2 NPTX1 NRA1 NRA3 NRP1 NTR1 NTR1 NTR1 NTR1 NTR1 NTR1 NTR1 NTR	NKAIN1	
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NTM NUAK2 NUP62CL NUP1 OR10H1 OR11H12 OR8M1 OR8M11 ORSM2 OSGIN2 OSTR PARD3 PARD3 PARD4 PDE40IP PDE5A PDCFRA PDLIM4 PDPR PD202 PEG10 PEL11 PGR PDTP2 PDE3A PDUM4 PDPR PDR PDR PDR PDR PDR PDR PDR PDPA PDF PDPA PDF PDR PDF PPARD PTTX2 PLA26	NRIP1	
NUA22 NUPE1 NUPL1 OR10H1 OR11H12 OR11 OR32 OR3811 OR392 OSGIN2 OXTR P2RY6 PARP14 PDE5A PDE5A PDGFRA PDIM4 PDE10 PE10 PE11 PRR PDTPR PDZD2 PE610 PE11 PGR PITPNC1 PTX2 PLA1A PL264 POUSF2 PPA2B PRX1 PRX2 PTX3 RASGRF1 RASGRF1	NTN1	
NUPE2CL NUPE1 OR10H1 OR11H12 OR1F1 OR2M2 ORSM11 ORSP2 OSGIN2 PARD3 PARD4 PDE5A PDE5A PDE51 PITNC1 PITN2 PLA1A PLCB4 POUSF2 PPRP PRNS PREX1 PSMD5 PITSF <td></td> <td></td>		
NUP1 OR10H1 OR11H2 OR11H2 OR2M2 ORSM11 OR5P2 OSGIN2 OXTR P2RY6 PARD3 PARP14 PDE40IP PDE5A PDOFRA PDUM4 PDPR PDZD2 PE610 PEL11 PQR PDZD2 PE610 PEL11 PQR PDIM4 PDPR PDITPNC1 PITX2 PLA1A PLA264A PL264A POU5F2 PPAP2B PRNS PRRX1 PSMD5 PTGFR PTGS2 PTFRC PTS2 PTAP2B PRNS PREX1 PSMD5 PTGFR PTGS2 PTFRC		
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OR1H142 OR1F1 OR2M2 ORSM11 ORSP2 OSGIN2 OXTR P2RY6 PARP14 PDE4DIP PDE5A PDCFRA PDIM4 PDE702 PE11 PGR PDZ02 PE11 PGR PITPNC1 PITX2 PLA1A PLA2G4A PLC84 POU5F2 PPAP2B PRNS PRRX1 PSMD5 PTGFR PTGS2 PTTRC PTTSR PTGS2 PTTSR PTGS2 PTTSR PTGS2 PTTSR PTGS2 PTTSR PTSR PTGSR PTGSR PTGSR PTGSR PTGSR PTGSR PTGSR PTGSR PTGSR <td></td> <td></td>		
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ORSFP2 OSGIN2 OXTR P2RY6 PARD3 PARP14 PDE4DIP PDE5A PDGFRA PDLIM4 PDPR PDZD2 PEL11 PGR PITNC1 PITX2 PLA1A PL2G4A PL02B4 POUSF2 PPA2B PRINS PRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RAB11FIP4 RASSF3 RC3H1 RCAN1 RCS16		
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PDE4DIP PDE5A PDGFRA PDLIM4 PDPR PDZ02 PEG10 PEL11 PGR PITPNC1 PITX2 PLA264A PLCB4 POUSF2 PPAP2B PRX1 PSMD5 PTGRC PTGS2 PTGRR PTGS3 RAB11FIP4 RASGRP1 RASGRP1 RCSD1 REL REL REL REL REL REL REJ RGS16		
PDE5A PDGFRA PDLM4 PDPR PDZD2 PEG10 PEL11 PGR PITPNC1 PITPX2 PLA1A PLCB4 POUSF2 PPAP2B PRINS PRRX1 PSS2 PTGFR PTGS2 PTTRC PTTS3 RAB11FIP4 RASSF3 RC3H1 RCAN1 RCSD1 REL		
PDGFRA PDIM4 PDPR PDDZ02 PEG10 PEL11 PGR PITPNC1 PITX2 PLA1A PLA2G4A PLOBF2 PPAP2B PRINS PRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RAB11FIP4 RASGRP1 RASGRP1 RCSN1 REL REL REL REL REL REJ RGS16		
PDLIM4 PDPR PDZD2 PEG10 PEL11 PGR PITPNC1 PITPX2 PLA1A PLCB4 POU5F2 PPAP2B PRX1 PSMD5 PTRC PTS3 RAB11FIP4 RASSF3 RC3H1 RCSD1 REL REL REL REL REL RES16		
PDPR PDZD2 PEG10 PEL11 PGR PITPNC1 PITX2 PLA1A PLZG4A PLCB4 POU5F2 PPAP2B PRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RASBR91 RASSF3 RC3H1 RCSD1 REL REL REL REL REJ RGS16	PDGFRA	
PDPR PDZD2 PEG10 PEL11 PGR PITPNC1 PITX2 PLA1A PLZG4A PLCB4 POU5F2 PPAP2B PRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RASBR91 RASSF3 RC3H1 RCSD1 REL REL REL REL REJ RGS16	PDLIM4	
PDZD2 PEG10 PEL11 PGR PITPNC1 PITX2 PLA1A PLCB4 POU5F2 PPAP2B PRNS PRX1 PRX1 PSMD5 PTGFR PTGFR PTGS2 PTPRC PTPRC PTPRC PTPRC PTX3 RAB11FIP4 RASSF3 RCSD1 RCSD1 REL REL REL REL RES RGS16		
PEG10 PEL11 PGR PITPNC1 PITX2 PLA1A PLA2G4A PLCB4 POU5F2 PPAP2B PRINS PRRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RAB11FIP4 RASSF3 RCSD1 REL REL REL REL REL REL RELB RFPL4B RGS16		
PEL11 PGR PITPNC1 PITX2 PLA1A PLA2G4A POU5F2 PPAP2B PRINS PRRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RABI1FIP4 RASSF3 RC3H1 RCSD1 REL REL REL REL REL REL REB RFPL4B RGS16		
PGR PITPNC1 PITX2 PLA1A PLA2G4A PLCB4 POU5F2 PPAP2B PRINS PRRX1 PSMD5 PTGFR PTRC PTRC PTX3 RAB11FIP4 RASSF3 RCSD1 REL REL REL REL REL REB RFPL4B RGS16		
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PLA1A PLA2G4A PLCB4 POU5F2 PPAP2B PRINS PRRX1 PSMD5 PTGFR PTGS2 PTRC PTX3 RAB11FIP4 RASSF3 RC3H1 RCSD1 REL REL RELB RFPL4B RGS16		
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PLCB4 POU5F2 PPAP2B PRINS PRRX1 PSMD5 PTGFR PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCSD1 REL RELB RFPL4B RGS16	PLA2G4A	
POU5F2 PPAP2B PRINS PRRX1 PSMD5 PTGFR PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCSD1 REL RELB RFPL4B RGS16		
PPAP2B PRINS PRRX1 PSMD5 PTGFR PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 REL REL REL RELB RFPL4B RGS16		
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PRRX1 PSMD5 PTGFR PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL RELB RFPL4B RGS16		
PSMD5 PTGFR PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL RELB RFPL4B RGS16		
PTGFR PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL REL RELB RFPL4B RGS16		
PTGS2 PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL RELB RFPL4B RGS16		
PTPRC PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL RELB RELB RFPL4B RGS16		
PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL RELB RFPL4B RGS16		
PTX3 RAB11FIP4 RASGRP1 RASSF3 RC3H1 RCAN1 RCSD1 REL RELB RFPL4B RGS16	PTPRC	
RAB11FIP4RASGRP1RASSF3RC3H1RCAN1RCSD1RELRELBRFPL4BRGS16		
RASGRP1RASSF3RC3H1RCAN1RCSD1RELRELBRFPL4BRGS16		
RASSF3RC3H1RCAN1RCSD1RELRELBRFPL4BRGS16		
RC3H1 RCAN1 RCSD1 REL RELB RFPL4B RGS16		
RCAN1 RCSD1 REL RELB RFPL4B RGS16		
RCSD1 REL RELB RFPL4B RGS16		
REL RELB RFPL4B RGS16		
RELB RFPL4B RGS16		
RELB RFPL4B RGS16		
RFPL4B RGS16		
RGS16		
RIPK2		
RLBP1		
RND1	RND1	

RNF157	
RRAD	
RSP03	
RTP4	
RUNX1	
S100A3	
SAMD4A	
SAMD9L	
SAMD9L	
SAV1	
SDC4	
SEC24A	
SELE	
SEMA3C	
SERPINA3	
SERPINB13	
SERPINB2	
SERPINE2	
SGPP2	
SHANK2	
SLC10A7	
SLC12A7	
SLC19A2	
SLC22A24	
SLC2A6	
SLC30A3	
SLC41A2	
SLC44A3	
SLC6A4	
SLC7A2	
SLC8A3	
SLC9A4	
SLCO4A1	
SLCO5A1	
SNORA60	
SNX3	
SOCS1	
SOD2	
SOX3	
SPINLW1	
SPON2	
SQRDL	
SRD5A2	
SSU72	
ST6GAL1	
ST8SIA2	
STAT5A	
STC2	
STON2	
SYT9	
TAP1	
TAS2R39	
ТСНН	
TFAP2A	
TGFB3	
THSD7B	
TIAM2	
TIFA	
TLR2	
TM4SF4	
TMCO2	
TMEM106A	
TMEM146	
TMEM146 TMEM217	
TMEM146 TMEM217 TMEM37	
TMEM146 TMEM217	

TNFAIP2	
TNFAIP3	
TNFAIP6	
TNFAIP8	
TNFRSF11B	
TNFRSF9	
TNFSF10	
TNFSF15	
TNFSF9	
TNIP1	
TNIP3	
TPPP	
TRAF1	
TRIM36	
TSLP	
TTC30A	
TTC39A	
UBD	
UBR4	
UGCG	
UMODL1	
UPP1	
VCAM1	
VEGFA	
VIPR2	
VSTM1	
WNT7B	
WTAP	
ZC3H12A	
ZC3H12C	
ZDHHC23	
ZFR2	
ZNF785	
2111700	

Supplementary Table 4. Regulated genes of drug and xenobiotic metabolism pathways significantly (P < 0.05) enriched in 4 h Wnt5A+IL-1 β transcriptome of HCAEC. Data are from 3 independent array experiments.

Gene symbol	Protein name	Class	Regulation
[†] ABTB2 ^a	Ankyrin repeat and BTB/POZ domain	Generic binding protein	Up
	containing protein 2	51	
[†] AMPD3 ^a	AMP deaminase 3	Generic enzyme	Up
[†] AQP9 ^e	Aquaporin-9	Generic channel	Down
[†] BCL2A1 ^a	Bcl-2-related protein A1	Generic binding protein	Up
[†] BDKRB2 ^{a,b,c}	B2 bradykinin receptor	GPCR	Up
[†] C1R ^b	Complement C1r subcomponent	Generic protease	Up
[†] C1S ^b	Complement C1s subcomponent	Generic protease	Up
[†] C3 ^b	Complement C3	Generic binding protein	Up
[†] CACNA1B ^a	Voltage-dependent N-type calcium channel subunit alpha-1B	Voltage-gated ion-channel	Up
CCL1 ^a	C-C motif chemokine 1	Receptor ligand	Up
[†] CCL2 ^{a,c}	C-C motif chemokine 2	Receptor ligand	Up
[†] CCL20 ^a	C-C motif chemokine 20	Receptor ligand	Up
[†] CCL4 ^a	C-C motif chemokine 4	Receptor ligand	Up
[†] CCL5 ^a	C-C motif chemokine 5	Receptor ligand	Up
CCL7 ^a	C-C motif chemokine 7	Receptor ligand	Up
[†] CCL8 ^b	C-C motif chemokine 8	Receptor ligand	Up
[†] CFB ^b	Complement factor B	Generic protease	Up
COX7B2 ^{a,b}	Cytochrome c oxidase subunit 7B2,	Generic enzyme	Down
	mitochondrial	-	
CSF2 ^b	Granulocyte-macrophage colony- stimulating factor	Receptor ligand	Up
[†] CSF3 [♭]	Granulocyte-macrophage colony- stimulating factor	Receptor ligand	Up
[†] CTSL ^b	Cathepsin L1	Generic protease	Up
[†] CXCL10 ^b	C-X-C motif chemokine 10	Receptor ligand	Up
* [†] CYP1A1 ^{a,c,f,g}	Cytochrome P450 1A1	Generic enzyme	Up
≠ [†] CYP7A1 ^{b,c,d,f}	Cytochrome P450 7A1	Generic enzyme	Up
[†] CYP1B1 ^{a,b,g}	Cytochrome P450 1B1	Generic enzyme	Up
DCHS2 ^a	Protocadherin-23	Generic binding protein	Down
†DNALI1 ^b	Axonemal dynein light intermediate polypeptide 1	Generic binding protein	Down
EBI3 ^a	Interleukin-27 subunit beta	Receptor ligand	Up
*†EDNRA ^{a,b,c}	Endothelin-1 receptor	GPCR	Up
[†] EFNA1 ^b	Ephrin-A1	Receptor ligand	Up
≠ [†] EPHA5°	Ephrin type-A receptor 5	Receptor with enzyme activity	Down
[†] FCGR2A ^a	Low affinity immunoglobulin gamma Fc	Generic receptor	Up
1	region receptor II-a		
[†] FILIP1L ^b	Filamin A-interacting protein 1-like	Generic protein	Up
[†] GBP1 ^{a,b}	Guanylate-binding protein 1	Generic binding protein	Up
[†] GCH1 ^a	GTP cyclohydrolase 1	Generic enzyme	Up
≠ [†] GNG2 ^{a,b}	Guanine nucleotide-binding protein	G beta/gamma	Down
	G(I)/G(S)/G(O) subunit gamma-2	0000	
[†] GPR37L1 ^{a,b,c}	G-protein coupled receptor 37-like 1	GPCR	Up
≠ [†] HOXB7 ^a	Homeobox protein Hox-B7	Transcription factor	Down
[†] ICAM1 ^{a,c,d}	Intercellular adhesion molecule 1	Generic receptor	Up
[†] IDO1 ^{a,b}	Indoleamine 2,3-dioxygenase 1	Generic enzyme	Up
≠ [†] IFNGR1 ^a	Interferon gamma receptor 1	Generic receptor	Up
≠ [†] IFNGR2 ^a	Interferon gamma receptor 2	Generic receptor	Up
[†] IL1B ^{a,b,c,d}	Interleukin-1 beta	Receptor ligand	Up
[†] IL6 ^{a,b,c,d}	Interleukin-6	Receptor ligand	Up
	Interleukin-10 receptor subunit alpha	Generic receptor	Up
[†] IRF1 ^a	Interferon regulatory factor 1	Transcription factor	Up
†ITGA4 ª	Integrin alpha-4	Generic receptor	Up
[†] KDM6B ^b	Lysine-specific demethylase 6B	Generic enzyme	Up
[†] KLF6 ^a	Krueppel-like factor 6	Transcription factor	Up
≠KLK3 ^{b,f}	Prostate-specific antigen	Generic protease	Up
[†] LAMB3 ^c	Laminin subunit beta-3	Receptor ligand	Up
[†] LAMC2 ^c	Laminin subunit gamma-2	Receptor ligand	Up

[†] LILRB4 ^b	Leukocyte immunoglobulin-like receptor subfamily B member 4	Generic receptor	Down
[†] MS4A2 ^b	High affinity immunoglobulin epsilon receptor subunit beta	Generic receptor	Up
[†] MTMR7 ^a	Myotubularin-related protein 7	Protein phosphatase	Up
MYB ^c	Transcriptional activator Myb	Transcription factor	Up
[†] NAB1 ^a	NGFI-A-binding protein 1	Transcription factor	Up
[†] NCOA7 ^a	Nuclear receptor coactivator 7	Generic binding protein	Up
[†] NFIB ^a	Nuclear factor 1 B-type	Transcription factor	Down
[†] NFKB1 ^a	Nuclear factor NF-kappa-B p105 subunit	Transcription factor	Up
[†] NINJ1 ^{a,b}		Generic binding protein	
	Ninjurin-1		Up
[†] NNMT ^{b,h}	Nicotinamide N-methyltransferase	Generic enzyme	Up
[†] NR4A3 [♭]	Nuclear receptor subfamily 4 group A member 3	Transcription factor	Up
[†] NTN1 ^a	Netrin-1	Receptor ligand	Up
OR10H1°	Olfactory receptor 10H1	GPCR	Up
OR1F1 ^c	Olfactory receptor 1F1	GPCR	Up
OR2K2 ^c	Olfactory receptor 2K2	GPCR	Down
OR2M2 ^c	Olfactory receptor 2M2	GPCR	Up
OR5L1°	Olfactory receptor 5L1	GPCR	Down
OR5M11°	Olfactory receptor 5M11	GPCR	Up
OR5P2°	Olfactory receptor 5P2	GPCR	Up
*OR9G4 ^c	Olfactory receptor 9G4	GPCR	Down
OXTR ^{a,b,c}	Oxytocin receptor	GPCR	Up
[†] PDE5A ^a	cGMP-specific 3',5'-cyclic	Generic enzyme	Up
	phosphodiesterase		~r
[†] PDGFRA ^{a,b,d}	Platelet-derived growth factor receptor	Receptor with enzyme	Up
	alpha	activity	
[†] PDLIM4 ^b	PDZ and LIM domain protein 4	Generic binding protein	Up
[†] PEG10 ^a	Retrotransposon-derived protein PEG10	Generic binding protein	Up
[†] PGR ^a	Progesterone receptor	Transcription factor	
			Up
≠ [†] PLA2G4A ^{a,b,g}	Cytosolic phospholipase A2	Generic phospholipase	Up
[†] PTGS2 ^{a,b,d}	Prostaglandin G/H synthase 2	Generic enzyme	Up
[†] REL ^a	Proto-oncogene c-Rel	Transcription factor	Up
[†] RELB ^a	Transcription factor RelB	Transcription factor	Up
≠RESP18 ^a	Regulated endocrine-specific protein 18	Generic protein	Down
[†] SAT1 ^b	Diamine acetyltransferase 1	Generic enzyme	Up
[†] SDC4 ^{a,b}	Syndecan-4	Generic receptor	Up
SLC22A2 ^e	Solute carrier family 22 member 2	Transporter	Down
SLC22A24 ^e	Solute carrier family 22 member 24	Transporter	Up
SLC6A4 ^e	Sodium-dependent serotonin transporter	Transporter	Up
[†] SLC7A2 ^e	Cationic amino acid transporter 2	Transporter	Up
[†] SLCO4A1 ^e			Up
'SLCO4A1°	Solute carrier organic anion transporter family member 4A1	Transporter	Up
[†] SOCS1 ^a	Suppressor of cytokine signaling 1	Generic binding protein	Up
[†] SOD2 ^ª	Superoxide dismutase [Mn], mitochondrial	Generic enzyme	Up
[†] STAT5A ^a	Signal transducer and activator of	Transcription factor	Up
	transcription 5A		
[†] STC2 ^ª	Stanniocalcin-2	Generic binding protein	Up
[†] SYT9ª	Synaptotagmin-9	Generic receptor	Up
TFAP2A ^d	Transcription factor AP-2-alpha	Transcription factor	Up
≠ [†] TGFB3 ^{a,b}	Transforming growth factor beta-3	Receptor ligand	Up
7" IGED3 ""	proprotein		oh
[†] TLR2 ^a	Toll-like receptor 2	Generic receptor	Up
[†] TNF ^{a,b,c,d}	Tumor necrosis factor	Receptor ligand	Up
[†] TNFAIP2 ^b	Tumor necrosis factor alpha-induced	Generic protein	Up
	protein 2		oh
≠ [†] TNFRSF9 ^b	Tumor necrosis factor receptor superfamily	Generic receptor	Up
	member 9		- 1
[†] TNFSF10 ^f	Tumor necrosis factor ligand superfamily member 10	Receptor ligand	Up
[†] VCAM1 ^a	Vascular cell adhesion protein 1	Generic receptor	Up
≠ [†] VEGFA ^b	Vascular endothelial growth factor A	Receptor ligand	Up
WNT7B ^a	Protein Wnt-7b	Receptor ligand	
VVINI/D-			Up

WW domain-containing transcription regulator protein 1		
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Genes regulated in AhR mediated regulation_heart^a

Genes regulated in LXR mediated regulation_heart^b

Genes regulated in PXR mediated regulation_heart^c

Genes regulated in FXR mediated regulation_heart^d

Genes regulated in Xenobiotic Metabolism. Phase III_heart^e

Genes regulated in CAR mediated regulation_heart^f

Genes regulated in Xenobiotic Metabolism. Phase I_heart^g

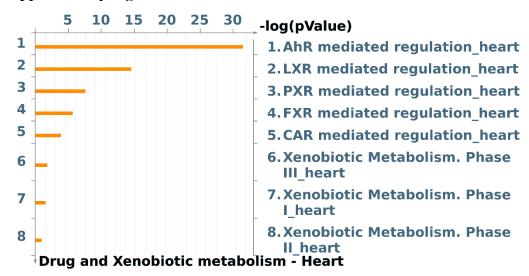
Genes regulated in Xenobiotic Metabolism. Phase II_hearth

*similarly regulated across Wnt5A, Wnt5A+IL-1, and IL-1^{\$} transcriptomes

≠regulated only in Wnt5A+IL-1 but not in Wnt5A or IL-1^{\$} transcriptomes

[†]Protein expression verified in normal human myocardium as shown in The Human Protein Atlas database (accessed on 03.08.2020)

[§]Genes of Drug and xenobiotic metabolism pathways most significantly (P < 0.05) regulated by 4 h IL-1 β treatment in HCAEC (Refer Supplementary Figure 1). Genes were identified by reanalysing data published in *Skaria, T., Bachli, E., and Schoedon, G. (2019). Gene Ontology Analysis for Drug Targets of the Whole Genome Transcriptome of Human Vascular Endothelial Cells in Response to Proinflammatory IL-1. Frontiers in Pharmacology 10.* The purpose of reanalysing data from above-said study was to identify the genes of myocardial drug and xenobiotic metabolism pathways regulated by 4 h IL-1 β treatment (which was not contained in previous study) that served as an additional positive control for comparing the effects of Wnt5A/ IL-1 β combination treatment with sole Wnt5A treatment in HCAEC.



Supplementary Figure 1

Supplementary Figure 1. Drug and xenobiotic metabolism pathways most significantly (P < 0.05) regulated by 4 h IL-1 β treatment in HCAEC. Pathways represented as histograms are ranked by the –log value (P value). This figure is generated by reanalysing data published in *Skaria, T., Bachli, E., and Schoedon, G. (2019). Gene Ontology Analysis for Drug Targets of the Whole Genome Transcriptome of Human Vascular Endothelial Cells in Response to Proinflammatory IL-1. Frontiers in Pharmacology 10.* The purpose of reanalysing data from above-said study was to identify the myocardial drug and xenobiotic metabolism pathways regulated by 4 h IL-1 β treatment (which was not contained in previous study) that served as an additional positive control for comparing the effects of Wnt5A/ IL-1 β combination treatment with sole Wnt5A treatment in HCAEC.