SUPPLEMENTAL MATERIAL

Exposure to inorganic arsenic and its methylated metabolites alters metabolomics profiles in INS-1 832/13 insulinoma cells and isolated pancreatic islets

Yuan-Yuan Li[1,2], Christelle Douillet[2], Madelyn Huang[3], Rowan Beck[4], Susan Jenkins Sumner[1,2,], Miroslav Styblo[2,3,*]*

[1]Nutrition Research Institute, Department of Nutrition, University of North Carolina at Chapel Hill School of Public Health, Chapel Hill, NC 27599, USA

[2]Department of Nutrition, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC 27599, USA

[3]Curriculum in Toxicology and Environmental Medicine, School of Medicine, University of North Carolina at Chapel Hill, NC 27599, USA (Currently: National Toxicology Program, National Institute of Environmental Health Science, Research Triangle Park, North Carolina)

[4]Curriculum in Genetics and Molecular Biology, School of Medicine, University of North Carolina at Chapel Hill, NC 27599, USA

Corresponding authors:

Miroslav Stýblo, PhD
Department of Nutrition, CB# 74612
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7461, USA
Phone: (919) 966-5721
styblo@med.unc.edu

Susan Jenkins Sumner, PhD
Nutrition Research Institute, Department of Nutrition, CB# 74612
Chapel Hill, NC 27599-7461, USA
Phone: 704-250-5066
Susan_sumner@unc.edu

Supplementary Table 1a. Metabolites perturbed in INS-1 832/13 cells exposed to iAs^{III} as compared to control (Ctrl)

Metabolite[a] (46 signals, 18 with annotation or identification)	Ontology level[b]	INS-1 832/13 cells exposed to iAs^{III} vs Ctrl		
		VIP[c]	*p*-value[d]	FC[e]
γ-Aminobutyric acid	OL1	2.0	0.002	-1.6
Acetylcarnitine	OL1	4.0	<0.001	-1.8
Succinic acid	OL1	2.2	0.005	-1.5
Betaine	OL2a	6.0	0.046	-1.3
Nicotinamide	OL2a	4.1	0.026	-1.3
Ribonolactone	PDc	1.2	<0.001	-1.8
2,3-Diketo-L-gulonate	PDc	2.3	0.001	-2.5
D-Glucaro-1,4-lactone	PDc	6.2	<0.001	-2.2
Glycylproline	PDc	1.0	<0.001	-2.5
Oxoglutarate	PDc	2.8	<0.001	-2.2
Acetylacrylate	PDc	1.4	0.005	-1.4
3b,17b-Dihydroxyetiocholane	PDc	1.0	0.039	2.1
Behenoylglycine	PDc	1.2	0.019	1.5
10-Hydroxy-2,8-decadiene-4,6-diynoic acid	PDd	1.1	<0.001	2.2
8-Hydroxyguanosine	PDd	1.8	<0.001	2.7
Thr-Phe-Arg	PDd	1.6	0.006	-2.6

[a]Cut-off criteria for signals/metabolites differentiating the arsenical treated group from control are VIP≥1.0 and $p<0.05$. [b]Ontology levels: OL1, highly confident identification based on matching with In-house physical standard library (IPSL) via retention time (RT, with RT error≤|0.5|), exact mass (MS, with mass error<5ppm), and tandem mass similarity (MS/MS, with similarity score≥30); OL2a, confident identification based on matching with IPSL via MS and RT; OL2b, annotation for the isomer or derivatives of the compound listed but not the compound itself, based on matching with IPSL via MS and MS/MS; PDa, annotation based on matching with public database via MS and experimental MS/MS (could be the listed compound, or the isomer or derivatives of the listed compound); PDb, annotation based on matching with public database via MS and predict MS/MS; PDc, annotation for the listed compound based on matching with public database via MS and isotopic similarity or adducts; PDd annotation for listed compound based on matching with public database via MS. [c]VIP, Variable influence on projections to latent structures. [d]p-value determined by *t*-test. [e]FC, fold change, the ratio of intensity between the arsenical treated INS-1 832/13 cells vs control INS-1, based on the mean, indicates the direction and magnitude of change: positive FC indicates increase compared to control and negative FC indicates decrease compared to control.

Supplementary Table 1b. Metabolites perturbed in INS-1 832/13 cells 1exposed to MAs^{III} as compared to control (Ctrl)

Metabolite[a] (109 signals, 29 with annotation or identification)	Ontology level[b]	INS-1 832/13 cells exposed to MAs^{III} vs Ctrl		
		VIP[c]	*p*-value[d]	FC[e]
Aspartic acid	OL1	4.1	<0.001	3.6
Glutamic acid	OL1	6.8	0.023	-1.5
Carnitine	OL1	1.9	0.001	1.3
N-Methyl-L-glutamic acid	OL1	5.9	<0.001	-2.5
Acetylcarnitine	OL1	3.3	<0.001	-1.6
Succinic acid	OL1	1.7	0.007	-1.4
Cyclic adenosine monophosphate	OL1	1.4	<0.001	2.5
O-Phosphorylethanolamine	OL2a	1.1	0.007	3.0
Raffinose	OL2a	1.0	0.008	-1.6
2'-Deoxyadenosine 5'-monophosphate	PDa	1.1	<0.001	-3.5
Glycerophosphocholine	PDb	14.0	0.015	1.6
Tyrosyl-Glutamine	PDb	1.7	<0.001	-3.5
Oxidized glutathione	PDb	17.5	<0.001	1.9
2-{[hydroxy(6-hydroxy-2H-1,3-benzodioxol-5-yl)methylidene]amino}acetic acid	PDb	1.0	<0.001	-2.9
Succinyladenosine	PDb	2.8	0.002	-3.4
N-Undecanoylglycine	PDc	3.4	0.019	1.8
Glycylproline	PDc	1.0	<0.001	-2.4
β-Glycerophosphate	PDc	1.5	<0.001	-7.9
Ribonolactone	PDc	1.3	<0.001	-2.2
3-Oxoglutaric acid	PDc	2.9	<0.001	-2.6
2,3-Diketo-L-gulonate	PDc	2.3	<0.001	-2.9
D-Glucaro-1,4-lactone	PDc	6.4	<0.001	-2.7
cis-Acetylacrylate	PDc	1.3	0.004	-1.3
3b,17b-Dihydroxyetiocholane	PDc	2.1	0.009	6.3
Thr-Leu	PDc	1.0	0.004	-1.6
8-Hydroxyguanosine	PDd	1.2	<0.001	1.9
Thr-Phe-Arg	PDd	1.8	0.002	-4.2

[a]Cut-off criteria for signals/metabolites differentiating the arsenical treated group from control are VIP≥1.0 and $p<0.05$. [b]Ontology levels: OL1, highly confident identification based on matching with In-house physical standard library (IPSL) via retention time (RT, with RT error≤|0.5|), exact mass (MS, with mass error<5ppm), and tandem mass similarity (MS/MS, with similarity score≥30); OL2a, confident identification based on matching with IPSL via MS and RT; OL2b, annotation for the isomer or derivatives of the compound listed but not the compound itself, based on matching with IPSL via MS and MS/MS; PDa, annotation based on matching with public database via MS and experimental MS/MS (could be the listed compound, or the isomer or derivatives of the listed compound); PDb, annotation based on matching with public database via MS and predict MS/MS; PDc, annotation for the listed compound based on matching with public database via MS and isotopic similarity or adducts; PDd annotation for listed compound based on matching with public database via MS. [c]VIP, Variable influence on projections to latent structures. [d]p-value determined by *t*-test. [e]FC, fold change, the ratio of intensity between the arsenical treated cells vs control cells, based on the mean, indicates the direction and magnitude of change: positive FC indicates increase compared to control and negative FC indicates decrease compared to control.

Supplementary Table 1c. Metabolites perturbed in INS-1 832/13 cells exposed to $DMAs^{III}$ as compared to control (Ctrl)

Metabolite[a] (456 signals, 98 with annotation or identification)	Ontology level[b]	INS-1 832/13 cells exposed to $DMAs^{III}$ vs Ctrl		
		VIP[c]	*p*-value[d]	FC[e]
Spermine	OL1	2.3	0.006	-1.7
Spermidine	OL1	2.3	0.017	-1.5
Ornithine	OL1	1.8	0.017	-1.8
Phosphorylcholine	OL1	3.2	0.025	-1.9
Alanine	OL1	1.5	<0.001	-2.2
Threonine	OL1	1.2	0.009	-1.3
Glutamic acid	OL1	4.3	0.030	-1.6
ɣ-Aminobutyric acid	OL1	1.1	0.003	-1.6
Creatine	OL1	12.1	<0.001	-3.0
Proline	OL1	4.9	<0.001	-1.4
Cytosine	OL1	1.7	<0.001	-3.0
N-Methyl-L-glutamic acid	OL1	4.1	<0.001	-7.3
Guanine	OL1	1.7	<0.001	-2.4
Acetylcarnitine	OL1	2.0	<0.001	-1.8
Glutathione reduced	OL1	6.4	0.007	-10.6
Methionine	OL1	6.4	0.024	-1.5
Hypoxanthine	OL1	5.6	<0.001	-2.7
Xanthine	OL1	1.7	0.008	-1.7
Succinic acid	OL1	1.4	<0.001	-1.8
Tyrosine	OL1	8.6	0.012	-1.7
Uridine	OL1	2.8	<0.001	-3.8
4-Hydroxyphenylpyruvic acid	OL1	1.1	0.010	1.4
S-Adenosyl-L-homocysteine	OL1	3.2	<0.001	-3.1
Serotonin	OL1	1.5	0.002	-1.9
Adenosine	OL1	2.0	0.001	2.7
Inosine	OL1	7.3	<0.001	-4.1
Guanosine	OL1	2.9	<0.001	-3.8
Phenylalanine	OL1	10.4	0.030	-1.5
Tryptophan	OL1	7.5	0.012	-1.7
Methylthioadenosine	OL1	1.9	0.001	-1.9
Suberic acid	OL1	1.5	0.009	1.4
Azelaic acid	OL1	2.3	0.006	1.4
5-Aminolevulinic acid	OL2a	1.2	0.042	-1.3
Cytidine	OL2a	3.5	<0.001	-3.6
Valine	OL2a	6.3	0.007	-1.4
Nicotinamide	OL2a	3.5	<0.001	-1.8
Leucine	OL2a	1.3	0.026	-1.8
N-Acetylneuraminic acid	OL2b	1.3	0.007	-1.9

Uracil	OL2b	1.6	<0.001	-3.1
Sphingosine	OL2b	1.6	0.022	1.3
Hypoxanthine	OL2b	5.9	<0.001	-3.7
Guanine	OL2b	1.8	<0.001	-3.8
4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid	PDa	11.2	0.042	-1.4
Uridine 5'-monophosphate	PDa	2.7	0.015	-2.0
Adenosine 5'-monophosphate	PDa	11.8	0.003	-2.3
Guanosine 5'-monophosphate	PDa	1.6	<0.001	-2.4
.beta.-Nicotinamide adenine dinucleotide	PDa	5.8	<0.001	-3.4
Cyclic adenosine diphosphate ribose	PDa	1.1	<0.001	-2.9
4-Hydroxybenzaldehyde	PDa	1.6	0.012	-1.6
2-Phenylacetamide	PDa	2.7	0.012	-1.7
Phenylpyruvic acid	PDa	1.1	0.012	-1.7
N-Acetyl-D-glucosamine	PDa	2.5	0.008	1.4
3-Hydroxyoctadecanoic Acid	PDa	3.9	0.031	1.4
Leu-Pro-Arg	PDa	1.3	0.001	-2.3
1H-Indole-4-carboxaldehyde	PDa	1.0	0.010	-1.7
Glycerophosphocholine	PDb	6.6	0.006	-2.0
4-Hydroxycitrulline	PDb	1.5	0.040	-3.7
Inosine 2'-phosphate	PDb	4.5	<0.001	-4.4
Tyrosyl-Glutamine	PDb	1.0	<0.001	-8.3
Beta-Citryl-L-glutamic acid	PDb	5.0	<0.001	-2.9
Oxidized glutathione	PDb	7.9	<0.001	-3.4
Armillaripin	PDb	1.4	<0.001	2.2
9,10,13-TriHOME	PDb	1.5	0.005	1.5
LysoPC(18:2(9Z,12Z))	PDb	1.0	0.022	-6.9
LysoPC(20:4(5Z,8Z,11Z,14Z))	PDb	1.5	0.049	-2.7
Succinyladenosine	PDb	1.6	<0.001	-4.5
3-Oxoglutaric acid	PDc	1.5	<0.001	-2.4
2,3-Diketo-L-gulonate	PDc	1.2	<0.001	-2.7
D-Glucaro-1,4-lactone	PDc	3.6	<0.001	-2.7
6-Hydroxypentadecanedioic acid	PDc	1.7	0.002	1.6
9,12,13-TriHOME	PDc	1.2	0.011	1.4
O2'-4a-cyclic-tetrahydrobiopterin	PDc	2.3	0.005	1.5
2-amino-6-hydroxyhexanoic acid	PDc	2.9	0.004	1.6
3-Oxooctadecanoic acid	PDc	1.3	0.010	1.4
xi-7-Hydroxyhexadecanedioic acid	PDc	1.0	0.008	1.5
2-Methoxyestrone	PDc	2.0	0.001	2.0
Ciliatine	PDc	8.0	0.007	1.4
O-Ureidohomoserine	PDc	2.0	0.012	1.4
Valyl-Threonine	PDc	1.4	0.007	1.5
2,3-Dihydro-5-(3-hydroxypropanoyl)-1H-pyrrolizine	PDc	1.6	<0.001	-2.7
Pro-Trp-Lys	PDc	2.2	0.003	1.7

Galactose-beta-1,4-xylose	PDc	1.8	0.003	-2.3
Ricinoleic acid	PDc	2.1	0.014	1.4
(3R,7R)-1,3,7-Octanetriol	PDc	2.0	0.045	1.3
N-Undecanoylglycine	PDc	1.7	0.005	1.5
2-{[3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-	PDc	2.1	0.006	1.3
11-Oxohexadecanoic acid	PDc	1.4	0.003	1.5
7-Methylguanosine	PDc	1.5	0.004	1.8
(2-Mercaptopropionylamino)acetic acid	PDd	2.6	<0.001	-3.2
Guanosine monophosphate	PDd	6.3	<0.001	-2.8
(4-{[2-methoxy-4-(prop-2-en-1-yl)phenoxy]carbonyl}phenyl)oxidanesulfonic acid	PDd	2.0	<0.001	-2.8
[(4-{5,14-dihydroxy-3-methoxy-8,17-dioxatetracyclo[8.7.0.0^{2},^{7}.0^{11},^{16}]heptadeca-1(10),2(7),3,5,11(16),12,14-heptaen-4-yl}-2-methylbut-2-en-1-yl)oxy]sulfonic acid	PDd	1.3	<0.001	2.7
3-Hydroxydodecanoic acid	PDd	2.3	0.011	1.4
Dihydrozeatin	PDd	1.2	0.003	1.5
1-Hexadecylamine	PDd	1.7	0.008	1.4
Histidinyl-Methionine	PDd	2.0	<0.001	-4.0
Thr-Phe-Arg	PDd	1.1	<0.001	-11.0
Cysteinyl-Histidine	PDd	1.0	0.007	1.4

[a]Cut-off criteria for signals/metabolites differentiating the arsenical treated group from control are VIP≥1.0 and p<0.05. [b]Ontology levels: OL1, highly confident identification based on matching with In-house physical standard library (IPSL) via retention time (RT, with RT error≤|0.5|), exact mass (MS, with mass error<5ppm), and tandem mass similarity (MS/MS, with similarity score≥30); OL2a, confident identification based on matching with IPSL via MS and RT; OL2b, annotation for the isomer or derivatives of the compound listed but not the compound itself, based on matching with IPSL via MS and MS/MS; PDa, annotation based on matching with public database via MS and experimental MS/MS (could be the listed compound, or the isomer or derivatives of the listed compound); PDb, annotation based on matching with public database via MS and predict MS/MS; PDc, annotation for the listed compound based on matching with public database via MS and isotopic similarity or adducts; PDd annotation for listed compound based on matching with public database via MS. [c]VIP, Variable influence on projections to latent structures. [d]p-value determined by *t*-test. [e]FC, fold change, the ratio of intensity between the arsenical treated cells vs control β-cells, based on the mean, indicates the direction and magnitude of change: positive FC indicates increase compared to control and negative FC indicates decrease compared to control.

Supplementary Table 2a. Metabolites perturbed in pancreatic islets exposed to iAs^{III} as compared to control (Ctrl)

Metabolite[a] (622 signals, 83 with annotation or identification)	Ontology level[b]	Islets exposed to iAs^{III} vs Ctrl		
		VIP[c]	*p*-value[d]	FC[e]
Taurine	OL1	1.5	0.27	-1.2
L-Aspartic Acid	OL1	1.1	0.51	-1.1
L-Glutamic Acid	OL1	1.5	0.93	-1.0
S-Adenosylmethionine	OL1	1.1	0.13	-1.5
Sucrose	OL1	1.6	0.39	2.3
Hypoxanthine	OL1	1.5	0.94	-1.0
Dl-Leucine	OL1	2.1	0.96	-1.0
Petroselinate	OL1	1.3	0.78	1.0
Suberate	OL1	1.2	0.76	1.0
Azelate	OL1	2.0	0.64	1.0
Galactose	OL2a	5.2	0.76	-1.1
Sorbitol	OL2a	1.0	0.24	2.5
Hypotaurine	OL2a	0.3	0.30	3.9
Orotic Acid	OL2a	0.2	0.02	-1.6
L-Valine	OL2a	1.7	0.57	-1.1
12-Hydroxydodecanoic Acid	OL2b	1.8	0.80	1.0
Dethiobiotin	OL2b	0.3	0.19	2.1
Suberate	OL2b	1.0	0.57	1.0
L-Tryptophanamide	OL2b	0.4	0.47	2.0
N-Palmitoylglycine	PDa	1.2	0.42	2.6
Uridine 5'-Monophosphate	PDa	1.3	0.27	-1.2
Thr-Pro	PDa	0.5	0.04	-1.2
N-Acetyl-D-Glucosamine	PDa	1.9	0.59	1.0
Lyso-PC(16:0)	PDa	1.0	0.71	1.1
Palmitamide	PDa	2.9	0.34	1.4
Uridine Diphosphate-N-Acetylglucosamine	PDb	1.0	0.22	-1.2
2-[(6-Carboxy-3,4,5-Trihydroxyoxan-2-Yl)Oxy]-3-	PDb	0.5	0.17	-4.4
Oxidized Glutathione	PDb	5.7	0.03	1.3
Lysope(20:4(8Z,11Z,14Z,17Z)/0:0)	PDb	1.8	0.89	1.0
Lysope(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)	PDb	1.3	0.83	-1.1
Linoleamide	PDb	1.7	0.68	1.3
4-Hydroxydebrisoquine	PDb	0.3	0.02	-1.3
Mevalonic Acid	PDb	1.3	0.39	4.4
Androsterone Sulfate	PDb	1.1	0.36	2.0
11-Oxohexadecanoic Acid	PDc	1.2	0.62	1.0
3-Sulfopyruvic Acid	PDc	3.6	0.60	1.0
Oxoglutarate	PDc	0.5	0.04	-2.2
4-(Glutamylamino) butanoate	PDc	0.7	0.01	1.6
6-Dimethylaminopurine	PDc	0.6	0.26	2.1

Isobutyryl-L-carnitine	PDc	0.8	0.34	6.9
4,8 Dimethylnonanoyl carnitine	PDc	1.1	0.48	2.2
N-Lauroylglycine	PDc	0.6	0.31	2.0
PE(P-16:0e/0:0)	PDc	0.2	0.56	-2.6
L-Octanoylcarnitine	PDc	0.6	0.25	2.3
Palmitoylglycine	PDc	2.7	0.48	2.5
5'-Deoxyadenosine	PDc	1.4	0.59	1.0
1,2-Dihexanoyl-sn-glycerol	PDc	1.0	0.80	1.0
Indanone	PDc	0.2	0.05	1.5
N-Acetyl-b-glucosaminylamine	PDc	1.5	0.74	1.0
(2Z)-2-[(2-hydroxyphenyl)methylidene]heptanal	PDc	0.3	<0.01	1.3
Palmitoleoyl Ethanolamide	PDc	6.9	0.40	2.9
4-(3,7-dimethylocta-2,6-dien-1-yl)benzene-1,2,3,5-tetrol	PDc	1.5	0.66	-1.0
Pro-Val-Arg	PDc	2.3	0.33	14.2
MG(0:0/i-12:0/0:0)	PDc	1.8	0.21	1.2
1,11-Undecanedicarboxylic acid	PDc	3.9	0.39	2.1
11-Hydroxyoctadecanoic acid	PDc	2.0	0.78	1.0
11beta-Hydroxy-3,20-dioxopregn-4-en-21-oic acid	PDc	0.4	0.03	1.1
3-Sulfopyruvic acid	PDc	1.9	0.70	1.0
3-Sulfopyruvic acid	PDc	2.0	0.67	1.0
Valyl-Threonine	PDc	1.0	0.66	1.0
Hydroxyprolyl-Isoleucine	PDc	1.2	0.60	1.0
gamma-Glutamylvaline	PDc	0.3	0.02	-1.6
N-Nonanoylglycine	PDc	0.3	0.41	5.5
Alanyl-Tyrosine	PDc	0.4	0.44	2.3
Formyl-5-hydroxykynurenamine	PDc	0.3	0.35	-3.3
N-Decanoylglycine	PDc	0.6	0.46	2.7
Isovalerylcarnitine	PDc	0.4	0.33	8.1
Propionylcarnitine	PDc	0.3	0.26	2.5
Tetrahydrobiopterin	PDc	0.3	0.18	2.3
3-Isopropylmalate	PDc	5.9	0.30	-1.2
DL-Indole-3-lactic acid	PDc	5.4	0.05	-1.4
N2-(3-Carboxy-2-hydroxy-1-oxopropyl)arginine	PDd	0.4	<0.01	-2.2
Biotinyl-5'-AMP	PDd	0.4	0.01	1.6
L-Octanoylcarnitine	PDd	0.4	0.48	2.3
MG(0:0/20:2(11Z,14Z)/0:0)	PDd	0.2	0.52	-3.1
LysoPC(P-18:0)	PDd	0.6	0.21	-3.7
7-Hydroxy-6-methyl-8-ribityl lumazine	PDd	1.3	0.98	-1.0
Cholestane-3,7,12,25-tetrol-3-glucuronide	PDd	1.5	0.26	1.1
Estrone sulfate	PDd	0.5	0.26	2.3
[(4-{5,14-dihydroxy-3-methoxy-8,17-dioxatetracyclo[8.7.0.0^{2},^{7}.0^{11},^{16}]heptadeca-1(10),2(7),3,5,11(16),12,14-heptaen-4-yl}-2-methylbut-	PDd	1.0	0.03	-1.3

6-[(17,19-Dioxo-5,7,9,20-tetraoxahexacyclo[11.7.0.02,10.03,8.04,6.014,18]icosa-1,10,12,14(18)-tetraen-12-yl)oxy]-3,4,5-	PDd	0.7	0.02	-1.4
4-Hydroxynonenal glutathione	PDd	0.5	0.09	2.1
Pivaloylcarnitine	PDd	0.3	0.33	2.8

[a]Cut-off criteria for signals/metabolites differentiating the arsenical treated group from control are VIP≥1.0 or $p<0.05$ or |FC|>2.0 (highlighted in red). [b]Ontology levels: OL1, highly confident identification based on matching with In-house physical standard library (IPSL) via retention time (RT, with RT error≤|0.5|), exact mass (MS, with mass error<5ppm), and tandem mass similarity (MS/MS, with similarity score≥30); OL2a, confident identification based on matching with IPSL via MS and RT; OL2b, annotation for the isomer or derivatives of the compound listed but not the compound itself, based on matching with IPSL via MS and MS/MS; PDa, annotation based on matching with public database via MS and experimental MS/MS (could be the listed compound, or the isomer or derivatives of the listed compound); PDb, annotation based on matching with public database via MS and predict MS/MS; PDc, annotation for the listed compound based on matching with public database via MS and isotopic similarity or adducts; PDd annotation for listed compound based on matching with public database via MS. [c]VIP, Variable influence on projections to latent structures. [d]p-value determined by *t*-test. [e]FC, fold change, the ratio of intensity between the arsenical treated islets vs control islets, based on the mean, indicates the direction and magnitude of change: positive FC indicates increase compared to control and negative FC indicates decrease compared to control.

Supplementary Table 2b. Metabolites perturbed in pancreatic islets exposed to MAs^{III} as compared to control (Ctrl)

Metabolite[a] (457 signals, 65 with annotation or identification)	Ontology level[b]	Islets exposed to MAs^{III} vs Ctrl		
		VIP[c]	*p*-value[d]	FC[e]
L-Glutamic acid	OL1	2.0	0.92	-1.0
S-Adenosylmethionine	OL1	1.8	0.06	-1.9
L-Citrulline	OL1	0.7	0.18	-2.0
O-Acetylcarnitine	OL1	1.3	0.39	-1.2
Uric acid	OL1	0.6	0.53	2.3
Ophthalmate	OL1	0.4	0.03	1.5
L-Tyrosine	OL1	1.5	0.19	-1.1
Petroselinate	OL1	1.6	0.87	1.0
Glycerol-myristate	OL1	1.2	0.69	1.0
Methylthioadenosine	OL1	4.4	0.02	-1.6
Suberate	OL1	1.3	0.78	-1.0
Betaine	OL2a	0.8	0.27	-2.1
L-Lysine	OL2a	0.3	0.39	2.4
4-Imidazoleacrylic acid	OL2a	2.6	0.12	-2.2
12-Hydroxydodecanoic acid	OL2b	2.4	0.99	1.0
Adenine	OL2b	0.8	0.03	-1.2
Suberate	OL2b	1.4	0.68	1.0
N-Acetyl-D-glucosamine	PDa	2.2	0.80	1.0
2-[(6-carboxy-3,4,5-trihydroxyoxan-2-yl)oxy]-3-hydroxybutanedioic acid	PDb	0.6	0.13	-6.8
Oxidized glutathione	PDb	4.8	0.31	-1.2
LysoPE(20:4(8Z,11Z,14Z,17Z)/0:0)	PDb	2.4	0.85	-1.1
LysoPE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)	PDb	1.7	0.71	-1.1
3b,16a-Dihydroxyandrostenone sulfate	PDb	1.1	0.26	2.1
11-Oxohexadecanoic acid	PDc	1.5	0.67	1.0
19-Oxoandrost-4-ene-3,17-dione	PDc	3.7	0.47	1.1
3-Sulfopyruvic acid	PDc	4.3	0.72	1.0
7-Keto-8-aminopelargonic acid	PDc	4.1	0.53	1.5
3-(1-Pyrrolidinyl)-2-butanone	PDc	1.0	0.53	1.4
20-Carboxy-leukotriene B4	PDc	0.3	0.05	1.2
5'-Deoxyadenosine	PDc	1.5	0.84	1.0
1,2-Dihexanoyl-sn-glycerol	PDc	1.1	0.88	-1.0
Indanone	PDc	0.2	0.02	1.4
Octadecanedioic acid	PDc	2.2	0.68	-1.1
N-Acetyl-b-glucosaminylamine	PDc	1.7	0.99	-1.0
13,14-Dihydro PGF-1a	PDc	2.2	0.34	-1.2
4-(3,7-dimethylocta-2,6-dien-1-yl)benzene-1,2,3,5-tetrol	PDc	2.1	0.61	1.0
(R)-3-Hydroxy-hexadecanoic acid	PDc	1.1	0.55	1.0
1,11-Undecanedicarboxylic acid	PDc	3.2	0.03	-1.4
Alanyl-Threonine	PDc	1.9	0.49	1.1
11-Hydroxyoctadecanoic acid	PDc	2.6	0.80	1.0
1-pentadecanoyl-glycero-3-phosphate	PDc	1.0	0.65	1.0
3-Sulfopyruvic acid	PDc	2.2	0.88	1.0
3-Sulfopyruvic acid	PDc	2.2	0.94	1.0

LysoSM(d18:1)	PDc	0.3	0.03	1.2
Valyl-Threonine	PDc	1.2	0.90	1.0
Hydroxyprolyl-Isoleucine	PDc	1.4	0.90	1.0
2-Methylbutylamine	PDc	1.0	0.99	1.0
N-methylphenylalanine	PDc	0.9	0.24	-2.9
Proline betaine	PDc	0.2	0.30	-2.2
gamma-Glutamylvaline	PDc	0.4	0.04	-1.5
N-Nonanoylglycine	PDc	0.1	0.35	-6.3
cis-4-Hydroxycyclohexylacetic acid	PDc	1.2	0.80	1.0
8-Hydroxyguanosine	PDc	0.9	0.02	-1.6
Alanyl-Tyrosine	PDc	0.3	0.01	-1.5
Formyl-5-hydroxykynurenamine	PDc	0.5	0.36	-3.2
N-Decanoylglycine	PDc	0.2	0.34	-2.5
D-Glucuronic acid 1-phosphate	PDc	1.1	0.08	-1.4
DL-Indole-3-lactic acid	PDc	6.0	0.32	-1.2
(Â±)-3-Hydroxynonanoic acid	PDd	0.4	0.01	1.2
LysoPC(P-18:0)	PDd	0.8	0.24	-3.3
.alpha.-Estradiol	PDd	0.5	0.01	1.3
Cholestane-3,7,12,25-tetrol-3-glucuronide	PDd	1.2	0.69	1.0
Palmitoylglycine	PDd	0.2	0.03	-1.4
gamma-Glutamylisoleucine	PDd	1.6	0.02	-1.6
[(4-{5,14-dihydroxy-3-methoxy-8,17-dioxatetracyclo[8.7.0.0^{2},^{7}.0^{11},^{16}]heptadeca-1(10),2(7),3,5,11(16),12,14-heptaen-4-yl}-2-methylbut-2-en-1-yl)oxy]sulfonic acid	PDd	1.2	0.36	-1.1

[a]Cut-off criteria for signals/metabolites differentiating the arsenical treated group from control are VIP≥1.0 or p<0.05 or |FC|>2.0 (highlighted in red). [b]Ontology levels: OL1, highly confident identification based on matching with In-house physical standard library (IPSL) via retention time (RT, with RT error≤|0.5|), exact mass (MS, with mass error<5ppm), and tandem mass similarity (MS/MS, with similarity score≥30); OL2a, confident identification based on matching with IPSL via MS and RT; OL2b, annotation for the isomer or derivatives of the compound listed but not the compound itself, based on matching with IPSL via MS and MS/MS; PDa, annotation based on matching with public database via MS and experimental MS/MS (could be the listed compound, or the isomer or derivatives of the listed compound); PDb, annotation based on matching with public database via MS and predict MS/MS; PDc, annotation for the listed compound based on matching with public database via MS and isotopic similarity or adducts; PDd annotation for listed compound based on matching with public database via MS. [c]VIP, Variable influence on projections to latent structures. [d]p-value determined by *t*-test. [e]FC, fold change, the ratio of intensity between the arsenical treated islets vs control β-cells, based on the mean, indicates the direction and magnitude of change: positive FC indicates increase compared to control and negative FC indicates decrease compared to control.

Supplementary Table 2c. Metabolites perturbed in pancreatic islets exposed to $DMAs^{III}$ as compared to control (Ctrl)

Metabolites[a] (593 signals, 72 with annotation or identification)	Ontology level	Islets exposed to $DMAs^{III}$ vs Ctrl		
		VIP*	*p*-value**	FC***
3-(4-HYDROXYPHENYL)PYRUVATE	OL1	1.0	0.59	1.0
Uric acid	OL1	0.3	0.28	-2.3
L-Citrulline	OL1	0.5	0.13	-2.4
Suberate	OL1	1.2	0.95	1.0
Ornithine	OL1	0.2	0.05	-1.3
Glycerol-Myristate	OL1	2.0	0.27	-1.1
L-Glutathione reduced	OL1	2.2	0.32	-2.1
Petroselinate	OL1	1.5	0.85	1.0
Ophthalmate	OL1	0.3	0.03	1.4
O-Acetylcarnitine	OL1	1.3	0.28	-1.3
2,6-Diaminopimelic acid	OL2a	0.5	0.02	1.2
4-Imidazoleacrylic acid	OL2a	2.3	0.07	-2.7
Caprylate	OL2b	1.1	0.16	2.1
Suberate	OL2b	1.3	0.48	1.0
Sphinganine	OL2b	2.0	0.35	1.1
Adenosine 5'-monophosphate	PDa	6.0	0.83	-1.0
4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic	PDa	9.5	0.25	-1.2
N-Acetyl-D-glucosamine	PDa	2.3	0.59	1.0
Glycylprolylhydroxyproline	PDb	1.4	0.10	-1.3
Oxidized glutathione	PDb	4.7	0.09	-1.3
PIP2(16:0/16:1(9Z))	PDb	1.3	0.27	-1.2
LysoPE(20:4(8Z,11Z,14Z,17Z)/0:0)	PDb	2.2	0.52	-1.2
LysoPE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)	PDb	1.6	0.46	-1.2
Myristoylglycine	PDb	0.4	0.09	2.5
2-[(6-carboxy-3,4,5-trihydroxyoxan-2-yl)oxy]-3-	PDb	0.6	0.12	-8.1
1,2-Dihexanoyl-sn-glycerol	PDc	1.2	0.72	1.0
7-Keto-8-aminopelargonic acid	PDc	7.8	0.13	2.9
Tetrahydrobiopterin	PDc	0.4	0.09	3.8
cis-4-Hydroxycyclohexylacetic acid	PDc	1.1	0.70	1.0
6-Dimethylaminopurine	PDc	0.8	0.26	2.9
Isovalerylcarnitine	PDc	0.1	0.51	2.3
N-Acetyl-b-glucosaminylamine	PDc	1.7	0.75	1.0
5'-Deoxyadenosine	PDc	1.8	0.51	1.0
4a-Carbinolamine tetrahydrobiopterin	PDc	3.8	0.24	-1.2
CDP-glucose	PDc	0.5	0.05	-1.5
3-Sulfopyruvic acid	PDc	4.8	0.55	1.0
3-Sulfopyruvic acid	PDc	2.2	0.73	1.0
3-Sulfopyruvic acid	PDc	2.3	0.73	1.0
9,12,13-TriHOME	PDc	1.0	0.55	1.0

Proline betaine	PDc	0.2	0.30	-2.2
19-Oxoandrost-4-ene-3,17-dione	PDc	1.9	0.84	-1.0
Palmitoyl glucuronide	PDc	0.4	0.04	1.1
Imidazole acetol-phosphate	PDc	0.3	0.02	1.2
Formyl-5-hydroxykynurenamine	PDc	0.3	0.37	-3.0
Myristoylglycine	PDc	0.5	0.17	2.4
N-Decanoylglycine	PDc	5.9	0.12	2.5
N-Nonanoylglycine	PDc	5.3	0.12	2.8
N-Nonanoylglycine	PDc	0.8	0.15	2.3
N-Undecanoylglycine	PDc	6.5	0.13	1.6
Tridecanoylglycine	PDc	1.8	0.15	2.0
Tridecanoylglycine	PDc	0.5	0.02	-1.5
Alanyl-Threonine	PDc	1.0	0.93	-1.0
Hydroxyprolyl-Isoleucine	PDc	1.4	0.65	1.0
Histidinyl-Histidine	PDc	0.4	0.05	1.1
Valyl-Threonine	PDc	1.2	0.65	1.0
N-methylphenylalanine	PDc	1.9	0.38	4.7
11-Oxohexadecanoic acid	PDc	1.3	0.55	1.0
2-Carboxy-4-dodecanolide	PDc	0.3	0.03	-1.2
(+)-15,16-Dihydroxyoctadecanoic acid	PDc	1.1	0.10	1.1
2-Methylbutylamine	PDc	1.1	0.71	1.0
3-(1-Pyrrolidinyl)-2-butanone	PDc	1.9	0.13	2.7
11-Hydroxyoctadecanoic acid	PDc	2.5	0.67	1.0
4-(3,7-dimethylocta-2,6-dien-1-yl)benzene-1,2,3,5-	PDc	2.4	0.59	1.0
(2E)-1-(4-hydroxy-3-methoxyphenyl)-3-	PDc	1.1	0.10	-1.5
Phenol, 4-(2-aminoethyl)-	PDc	0.8	0.33	2.8
3a,16b-Dihydroxyandrostenone	PDd	1.8	0.11	2.6
PC(14:1(9Z)/24:0)	PDd	0.8	0.08	-3.0
Cholestane-3,7,12,25-tetrol-3-glucuronide	PDd	1.3	0.53	1.0
Ascorbyl stearate	PDd	0.7	0.02	-2.0
Angiotensin I	PDd	2.2	0.03	-1.9
MG(12:0/0:0/0:0)	PDd	0.2	0.03	1.1
2-amino-4-({1-[(carboxymethyl)-C-hydroxycarbonimidoyl]-2-[(2-hydroxy-5-oxo-1,7-diphenylhept-3-en-1-yl)sulfanyl]ethyl}-C-	PDd	0.5	0.02	-1.4

[a]Cut-off criteria for signals/metabolites differentiating the arsenical treated group from control are VIP≥1.0 or p<0.05 or |FC|>2.0 (highlighted in red). [b]Ontology levels: OL1, highly confident identification based on matching with In-house physical standard library (IPSL) via retention time (RT, with RT error≤|0.5|), exact mass (MS, with mass error<5ppm), and tandem mass similarity (MS/MS, with similarity score≥30); OL2a, confident identification based on matching with IPSL via MS and RT; OL2b, annotation for the isomer or derivatives of the compound listed but not the compound itself, based on matching with IPSL via MS and MS/MS; PDa, annotation based on matching with public database via MS and experimental MS/MS (could be the listed compound, or the isomer or derivatives of the listed compound); PDb, annotation based on matching with public database via MS and predict MS/MS; PDc, annotation for the listed compound based on matching with public database via MS and isotopic similarity or adducts; PDd annotation for listed compound based on matching with public database via MS. [c]VIP,

Variable influence on projections to latent structures. [d]p-value determined by *t*-test. [e]FC, fold change, the ratio of intensity between the arsenical treated INS-1vs control INS-1, based on the mean, indicates the direction and magnitude of change: positive FC indicates increase compared to control and negative FC indicates decrease compared to control.

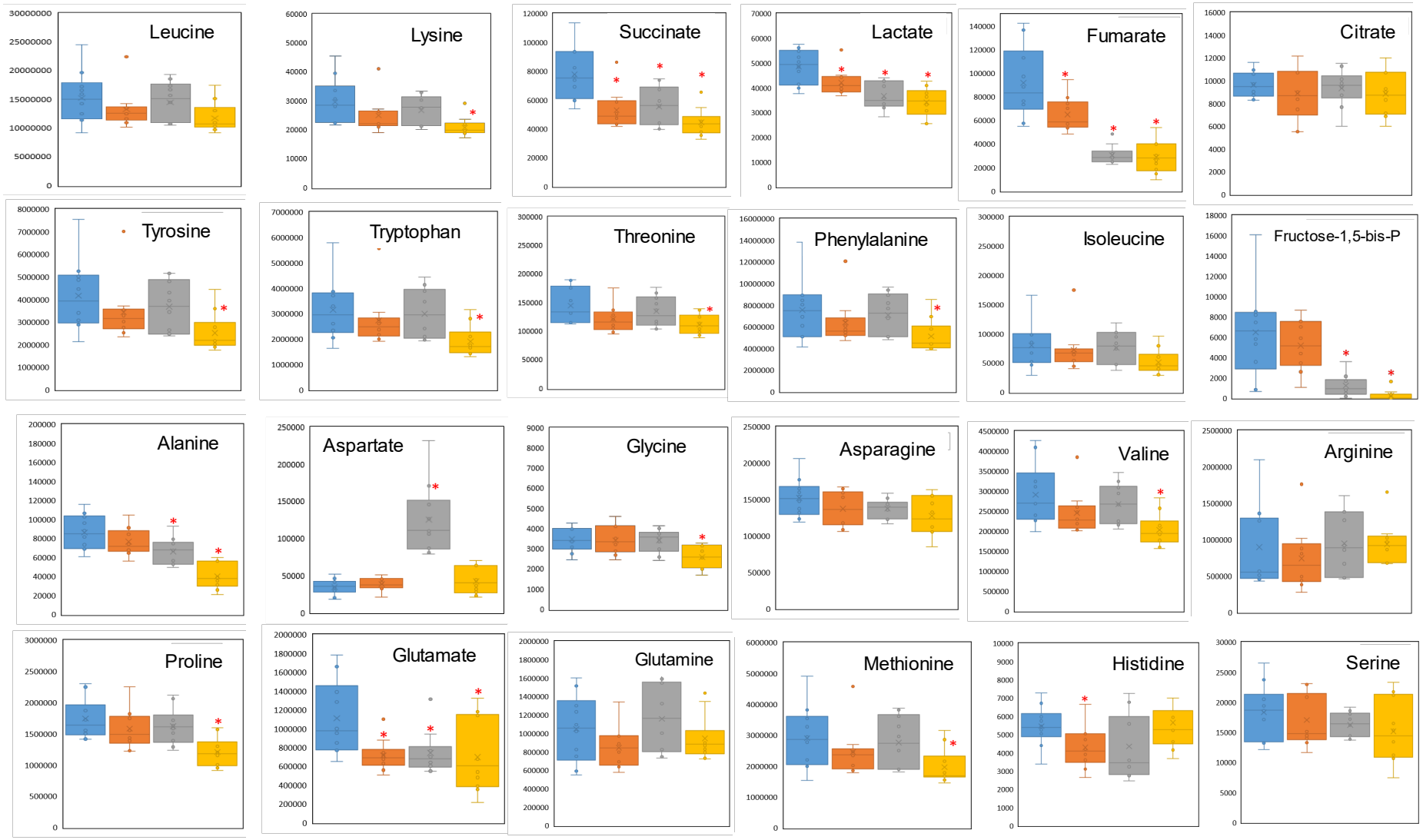
Supplemental Table 3. Metabolites perturbed in both INS-1 832/13 cells and pancreatic islets exposed to arsenicals as compared to the corresponding unexposed controls (Ctrl)

Code[a]	Metabolite[b]	FC in INS-1 832/13cells[c]			FC in Islets[c]		
		iAs^{III} vs Ctrl	MAs^{III} vs Ctrl	$DMAs^{III}$ vs Con	iAs^{III} vs Ctrl	MAs^{III} vs Ctrl	$DMAs^{III}$ vs Ctrl
A	Acetylcarnitine	-1.8	-1.6	-1.8		-1.2	-1.3
A	Glutamic acid		-1.5	-1.6	-1.0		
A	Aspartic acid		3.6		-1.1		
A	Glutathione reduced			-10.6			-2.1
A	Hypoxanthine			-2.7	-1.0		
A	Methylthioadenosine			-1.9		-1.6	
A	Leucine			-1.8	-1.0		
A	Ornithine			-1.8			-1.3
A	Valine			-1.4	-1.1		
A	4-Hydroxyphenylpyruvic acid			1.4			1.0
A	Azelaic acid			1.4	1.0		
A	Suberic acid			1.4	1.0	-1.0	1.0
A	Betaine	-1.3				-2.1	
B	5-Aminolevulinic acid			-1.3			
B	Adenosine			2.7			
B	Alanine			-2.2			
B	Creatine			-3			
B	Cytidine			-3.6			
B	Cytosine			-3			
B	ɣ-Aminobutyric acid			-1.6			
B	Guanine			-2.4			
B	Guanosine			-3.8			
B	Inosine			-4.1			
B	Methionine			-1.5			
B	Nicotinamide			-1.8			
B	N-Methyl-L-glutamic acid			-7.3			
B	Phenylalanine			-1.5			
B	Phosphorylcholine			-1.9			
B	Proline			-1.4			
B	S-Adenosyl-L-homocysteine			-3.1			
B	Serotonin			-1.9			
B	Spermidine			-1.5			
B	Spermine			-1.7			
B	Succinic acid			-1.8			
B	Threonine			-1.3			
B	Tryptophan			-1.7			
B	Tyrosine			-1.7			
B	Uridine			-3.8			
B	Xanthine			-1.7			
B	Carnitine		1.3				
B	Cyclic adenosine monophosphate		2.5				
B	N-Methyl-L-glutamic acid		-2.5				
B	O-Phosphorylethanolamine		3.0				
B	Raffinose		-1.6				
B	Succinic acid		-1.4				

B	ɣ-Aminobutyric acid	-1.6					
B	Nicotinamide	-1.3					
B	Succinic acid	-1.5					
C	2,6-Diaminopimelic acid						1.2
C	4-Imidazoleacrylic acid					-2.0	-2.7
C	Citrulline					-2.0	-2.4
C	Glyceryl monomyristate						-1.1
C	Ophthalmic acid						1.4
C	Petroselinic acid				1.0	1.0	1.0
C	Uric acid					2.3	-2.3
C	4-Imidazoleacrylic acid					-2.2	
C	Citrulline					-2.0	
C	Glutamic acid					-1.0	
C	Glyceryl monomyristate					1.0	-1.1
C	Lysine					2.4	
C	Ophthalmic acid					1.5	1.4
C	Petroselinic acid				1.0	1.0	1.0
C	S-Adenosyl-L-methionine				-1.5	-1.9	
C	Tyrosine					-1.1	
C	Uric acid					2.3	
C	Galactose				-1.1		
C	Hypotaurine				3.9		
C	Lyso-PC(16:0)				1.1		
C	N-Palmitoylglycine				2.6		
C	Orotic acid				-1.6		
C	Palmitamide				1.4		
C	Petroselinic acid				1.0		
C	S-Adenosyl-L-methionine				-1.5		
C	Sorbitol				2.5		
C	Sucrose				2.3		
C	Taurine				-1.2		
C	Thr-Pro				-1.2		

[a]The capital letters (A, B, C) correspond to the sections in Venn diagram in Figure 7. [b]The criteria for identification of differentially altered metabolites were VIP≥ 1.0 and $p<0.05$ for INS-1 832/13 cells and VIP≥ 1.0 or $p<0.05$ or $|FC|>2.0$ for the islets. [c]FC, fold change, the ratio of intensity between the arsenical-treated vs control INS-1 832/13 cells or islets, based on the mean, indicates the direction and magnitude of the metabolites impacted by arsenical treatments; positive FC indicates increase compared to control (highlighted in red) and negative FC indicates decrease compared to control (highlighted in blue). Lack of FC value (gray area) indicates that the metabolite did not satisfy the above criteria.

Supplemental Figure 1: Relative concentrations of metabolites in glucose-amino acid pathways in INS-1 832/13 -cells exposed to iAs^{III} (orange), MAs^{III} (gray) or $DMAs^{III}$ (yellow), and in untreated control cells (blue); * metabolite concentration in the exposed cells is significantly different ($p<0.05$) from that in control cells. Median (—), mean (x), 25th and 75th percentile (box), and individual values (○), including outliers (●) are shown; outliers are defined as values <Q1-1.5xIQR (bottom vertical line) or values >Q3+1.5xIQR (upper vertical line).



Supplemental Figure 2: Relative concentrations of carnitine and acylcarnitines in INS-1 832/13 cells exposed to iAs^{III} (orange), MAs^{III} (gray) or $DMAs^{III}$ (yellow), and in untreated control cells (blue); *metabolite concentration in the exposed cells is significantly different ($p<0.05$) from that in control cells. Median (—), mean (x), 25th and 75th percentile (box), and individual values (○), including outliers (●) are shown; outliers are defined as values <Q1-1.5xIQR (bottom vertical line) or values >Q3+1.5xIQR (upper vertical line).