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Supplementary Materials for

Interactions with stromal cells promote a more oxidized cancer cell redox state in pancreatic tumors

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Supplementary figure legends

Supplementary Figure 1. **Schematic representation of transwell, organoid monoculture, and organoid co-culture systems.** In the transwell system, PDAC cells cultured as 3D organoids embedded in Matrigel are in the bottom chamber while cells grown in 2D culture are in the upper chamber (transwell insert). In organoid monoculture, PDAC cells alone are cultured as 3D organoids embedded in Matrigel. Where indicated, exogenous alanine or pyruvate is added to the culture medium. In organoid co-culture, PDAC cells are cultured as 3D organoids and mixed with either MEFs or PSCs and embedded in Matrigel.

Supplementary Figure 2. **Growth assessment of organoids with exogenous metabolites or in co-culture with PSCs and MEFs (a)** Heatmap of the difference in mean number of organoids for murine PDAC cells cultured as 3D organoids in monoculture, co-culture with MEFs (+MEF), or co-culture with PSCs (+PSC), without (control) or with exogenous 1mM alanine (+Ala) or 1mM pyruvate (+Py) supplemented in the media. First row, [+Ala] – [control], represents the difference in mean organoid number between cultures when media contains 1mM exogenous alanine and media without alanine or pyruvate (control). Second row, [+Py] – [+Ala], represents the difference in mean organoid number between cultures with 1mM pyruvate and 1mM alanine. Third row [+Py] – [control] represents the difference in mean organoid number between cultures with 1mM pyruvate and control. n=3 images were analyzed per condition. Corresponding data are also shown in Figure 1c-d. **(b)** Heatmap of the difference in mean number of organoids derived from murine PDAC cells in mono- and co-cultures grown without any exogenous metabolite (control), or with 1mM exogenous alanine (+Ala) or 1mM pyruvate (+Py). First row, [+MEF] – [mono], represents difference in organoid number between PDAC cells cultured as 3D organoids in co-culture with

MEFs and monoculture. Second row [+PSC] – [+MEF], represents the difference in organoid number between co-culture with PSC and co-culture with MEF. Third row, [+PSC] – [mono], represents the difference in organoid number between co-culture with PSCs and monoculture. n=3 images were analyzed per condition. Corresponding data is also shown in Figure 1c-d. **(c)** Number of organoids (Num. Organoids) quantified from brightfield images of PDAC cells cultured as 3D organoid monoculture (mono-) grown in media without exogenous alanine or pyruvate (control), media supplemented with 1 mM alanine (+Ala) or 1 mM pyruvate (+Py). Also plotted are the number of PDAC cells cultured as 3D organoids, co-cultured (co-) with MEFs (+MEF) or PSCs (+PSC) as indicated. 3 independent wells were assessed per condition and each point is the average organoid number measured per well. n=3 per condition. Error bars represent the standard deviation. Data presented here are a subset of the data shown in Figure 1c. **(d)** The area of PDAC organoids cultured as 3D organoids alone (monoculture), co-cultured with MEF cells (+MEF) or PSCs (+PSC) with media supplemented with and without 1 mM pyruvate and 1 mM alanine as indicated. Area of each organoid was quantified from brightfield images (n=3 images per condition). 3 independent wells were assessed per condition. Each data point is an organoid area. **(e)** The number of organoids (Num.Organoids) or **(f)** organoid area of PDAC cells cultured as 3D organoids cultured alone without pyruvate (-Py), alone with 10mM exogenous pyruvate (+Py), co-cultured with MEFs (+MEF), co-cultured with immortalized PSCs (+PSC4, +PCS5), or co-cultured with primary PSCs (+primary PSC). The data is quantified from brightfield images of 4 dishes per condition (n=4 images analyzed per condition). Statistical significance of differences between multiple conditions for data presented in (a-f) were tested using one-way ANOVA with posthoc Tukey's test (*** $p< 0.001$; ** $p< 0.01$; * $p< 0.05$). Error bars for (e) represent the 95% confidence interval. (**g** and **h**) Proliferation of 2 different PSC lines (PSC5 in (g); PSC4 in (h)) in

either monoculture or co-culture with PDAC cells cultured as 3D organoids. GFP fluorescence was measured daily for 7 days. Plotted data represent mean fluorescence from 5 independent wells +/- standard deviation. A.U- arbitrary units.

Supplementary Figure 3. **Biochemical redox measurements of cells and optical imaging of PDAC organoids in mono-culture or in co-culture with PSCs** (**a**) NADH/NAD^+ measurements of indicated cancer cell lines (PDAC) or indicated PSCs under standard culture conditions with or without pyruvate. 3731 cell line was derived from the KPC model, while remaining PDAC lines were derived from the $KP^{-/-}C$ model; Technical replicates depicted with mean+/- std. **(b)** Optical redox ratio of 2D monocultures and co-cultures of unlabeled murine PDAC cells ($KP^{-/-}C$ mouse model) and immortalized unlabeled PSC cells measured 24 hours after plating (2 independent cultures per condition were assessed). The optical redox ratio for all the conditions were calculated at single cell level (PDAC cells monoculture: n=227; PDAC cells co-culture: n=91; PSC cells monoculture: n=265; PSC cells co-culture: n=119). The quantified data were normalized to the optical redox ratio for PDAC cells in monoculture. Data shown are derived from data that are presented in Figure 2 a-d. **(c)** Top panel shows representative fluorescence intensity images of NAD(P)H fluorescence (white) of 2D monocultures of PDAC cells ($KP^{-/-}C$ mouse model) and immortalized PSCs (PSC) and 2D co-culture of YFP+ murine PDAC cells ($KP^{-/-}C$ mouse model, labeled PDAC) and unlabeled PSCs. Cells were imaged after co-culture for 48 hours, and YFP (red) allowed specification of the cancer cells in co-culture. Corresponding optical redox ratio images are also shown (bottom). **(d)** Quantification of the optical redox ratio of PDAC cells (n=436) and PSCs (n=293) in monoculture, and unlabeled PSCs in co-culture (co-) (n=380) as described in (b) from 2 independent cultures per conditions. The quantified data was normalized to the optical redox ratio for PDAC cells in monoculture. **(e)** Representative fluorescence intensity

images of NAD(P)H fluorescence (white) of 2D monoculture of unlabeled PDAC cells (KPC mouse model), monoculture of unlabeled PSCs, co-culture of PDAC cells and GFP+ PSCs (labeled PSC), and co-culture of tdTomato+ PDAC cells (labeled PDAC, KPC mouse model) and unlabeled PSCs (top), cultured for 48 hours. Two separate co-cultures were prepared with one labeled and one unlabeled cell type, and optical redox ratios were assessed in the unlabeled cell type to circumvent interference of fluorescent labels with FAD signal. GFP intensity is overlaid in green and tdTomato in red with NAD(P)H intensity image in white. The optical redox ratio is also shown for all images (bottom). **(f)** Quantification of optical redox ratio from panel (c). n=8 images for monocultures and n=18-19 images for co-cultures were acquired from 2 independent cultures per condition and normalized to the mean optical redox ratio measured for PDAC cells in monoculture. For co-cultures, the optical redox ratios of unlabeled cells were computed, i.e, unlabeled PDAC cells with labeled PSCs excluded, or unlabeled PSCs with labeled PDAC cells excluded. The optical redox ratio was obtained at a single cell level (PDAC cell monoculture: n=1194; PDAC cell co-culture: n=1307; PSC monoculture: n=642; PSC co-culture: n=874). The statistical significance of differences between conditions shown in (b), (d) and (f) were evaluated using ANOVA with posthoc Tukey's test (*** $p< 0.001$; ** $p< 0.01$; * $p< 0.05$).

Supplementary Figure 4. Optical redox measurements of organoids over time and correlation with media pyruvate to lactate ratio (a) Heatmap of the difference in means in number of organoids for PDAC cells cultured as organoids from day 1 through 4. Each row represents difference of organoid number between two culture conditions (i.e., either monoculture or co-culture with PSC, supplemented with and without 10mM pyruvate (Py) as indicated). n=4 images were analyzed per condition. Corresponding data are also shown in Figure 3b. **(b)** Heatmap of the difference in mean organoid number for co-culture and monoculture, supplemented with

and without 10mM pyruvate (Py) as indicated. Each row represents difference in organoid number between two culture days. n=4 images were analyzed per condition. Corresponding data are also shown in Figure 3b. The statistical significance for (a) and (b) was tested using one-way ANOVA with posthoc Tukey's test (*** $p< 0.001$; ** $p< 0.01$; * $p< 0.05$). **(c)** Heatmap of the difference in means of optical redox ratio between PDAC cells and PSCs [PDAC – PSC], supplemented with or without 10mM pyruvate (Py) and grown as monoculture (mono-) or co-culture (co-) 3D organoids. n=6 images were analyzed per condition. Corresponding data are also shown in Figure 3e. **(d)** Optical redox ratio differences between monoculture and co-culture of PDAC cells cultured as 3D organoids, either supplemented with 10mM exogenous pyruvate or without pyruvate (Py) as indicated. Also plotted are differences in optical redox ratio between monoculture and co-culture of PSCs grown in 3D culture, either supplemented with 10mM exogenous pyruvate or without pyruvate. n=6 images were analyzed per condition. The optical redox ratio differences are plotted for day 1 through 4. The error bars represent the standard error. The data for days 2, 3, and 4 have been compared to day 1 using t-test for each curve (*** $p< 0.001$; ** $p< 0.01$; * $p< 0.05$). The data is derived from the data shown in Figure 3e **(e)** Quantification of optical redox ratios that were computed for each cell segmented from the PDAC cells cultured as 3D organoids in monoculture or co-culture with PSCs from day 1 through 4. Optical redox ratio was measured for the PDAC cells cultured in monoculture (mono-) or co-culture (co-) with the PSCs and PSCs grown in co-culture with the PDAC cells as 3D organoids. 2 dishes per culture condition were plated on each day from day 0 through day 3. All the n= 48 dishes were imaged on day 4 with at least n = 3 images per condition. Optical redox ratios for all the conditions have been normalized to PDAC cells in monoculture on day 1, grown without exogenous pyruvate. The statistical significance was tested using one-way ANOVA with posthoc Tukey's test (*** $p< 0.001$; ** $p<$

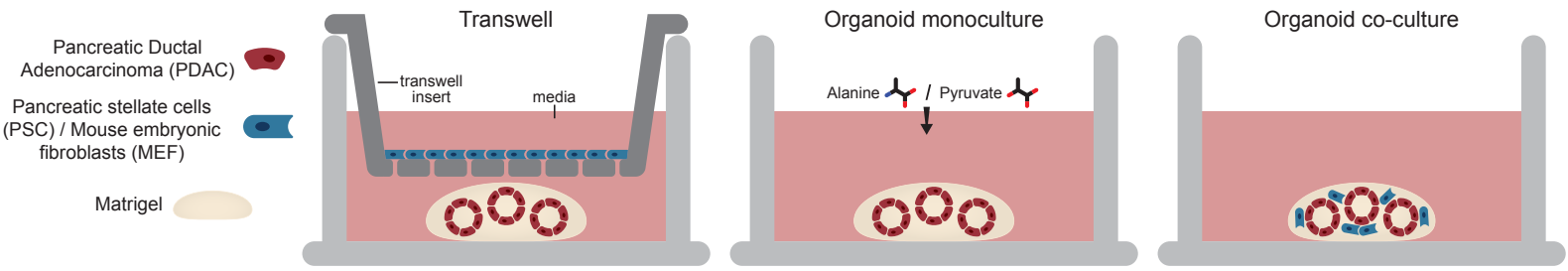
0.01). **(f)** Optical redox ratio (gray) and pyruvate to lactate ratio measured in media (yellow) for PDAC cells cultured as 3D organoids in monoculture (left panel), in co-culture with PSCs (middle panel), and PSC cells in co-culture with PDAC cells grown as 3D organoids (right panel). The optical redox ratio and pyruvate to lactate ratio were measured in cultures supplemented with and without 10mM exogenous pyruvate (Py). The measurements were performed on day 3 and 4 of culture. For optical redox ratio, at least n = 3 images were analyzed per condition and is a subset of data shown in (Supplementary Figure 4e). Optical redox ratio is normalized to the PDAC cells without pyruvate on day 1. Mean pyruvate and lactate measured per day was used to assess pyruvate to lactate ratio. Error bars represent the standard deviation.

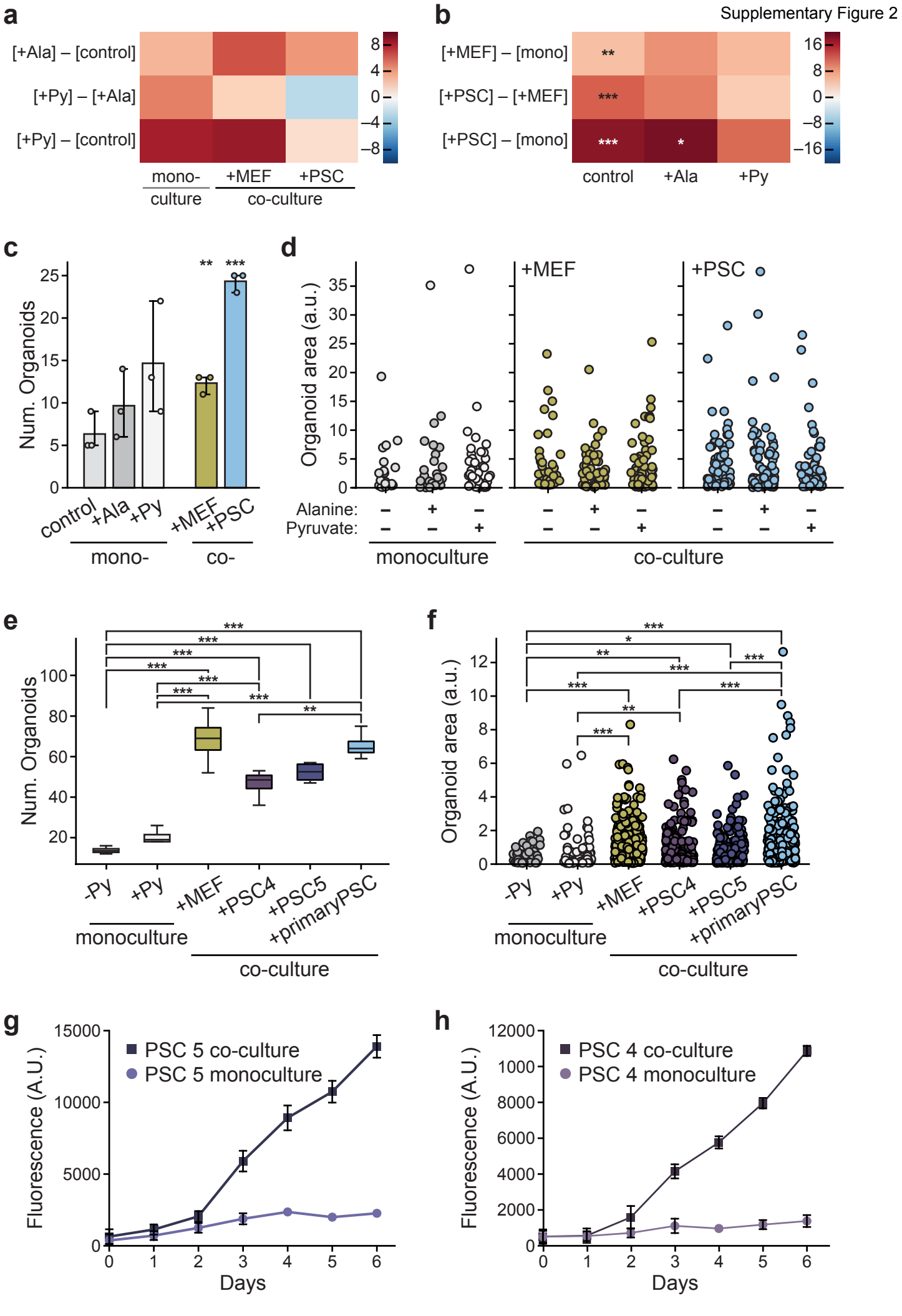
Supplementary Figure 5. Difference in metabolite levels measured by GC-MS in conditioned media from the indicated cells in culture compared to what is found in fresh culture media. Culture conditions evaluated include PDAC cells cultured as 3D organoids (PDAC), PSCs cultured in 3D (PSC), or PDAC cells cultured as 3D organoids in co-culture with PSCs (co-culture). Media was analyzed after 3 days of culture (left) or 4 days of culture (right) in DMEM-based media supplemented with or without (+/-) 10mM pyruvate as indicated. The score presented in the heatmap for each condition was generated by calculating the difference between each metabolite measured in conditioned media (observed) and that measured in fresh DMEM media alone (DMEM), normalized to the respective standard deviation of the metabolite levels measured for all conditions, i.e., respective metabolite row (σ_{row}). The raw data is provided in Supplementary Table 3.

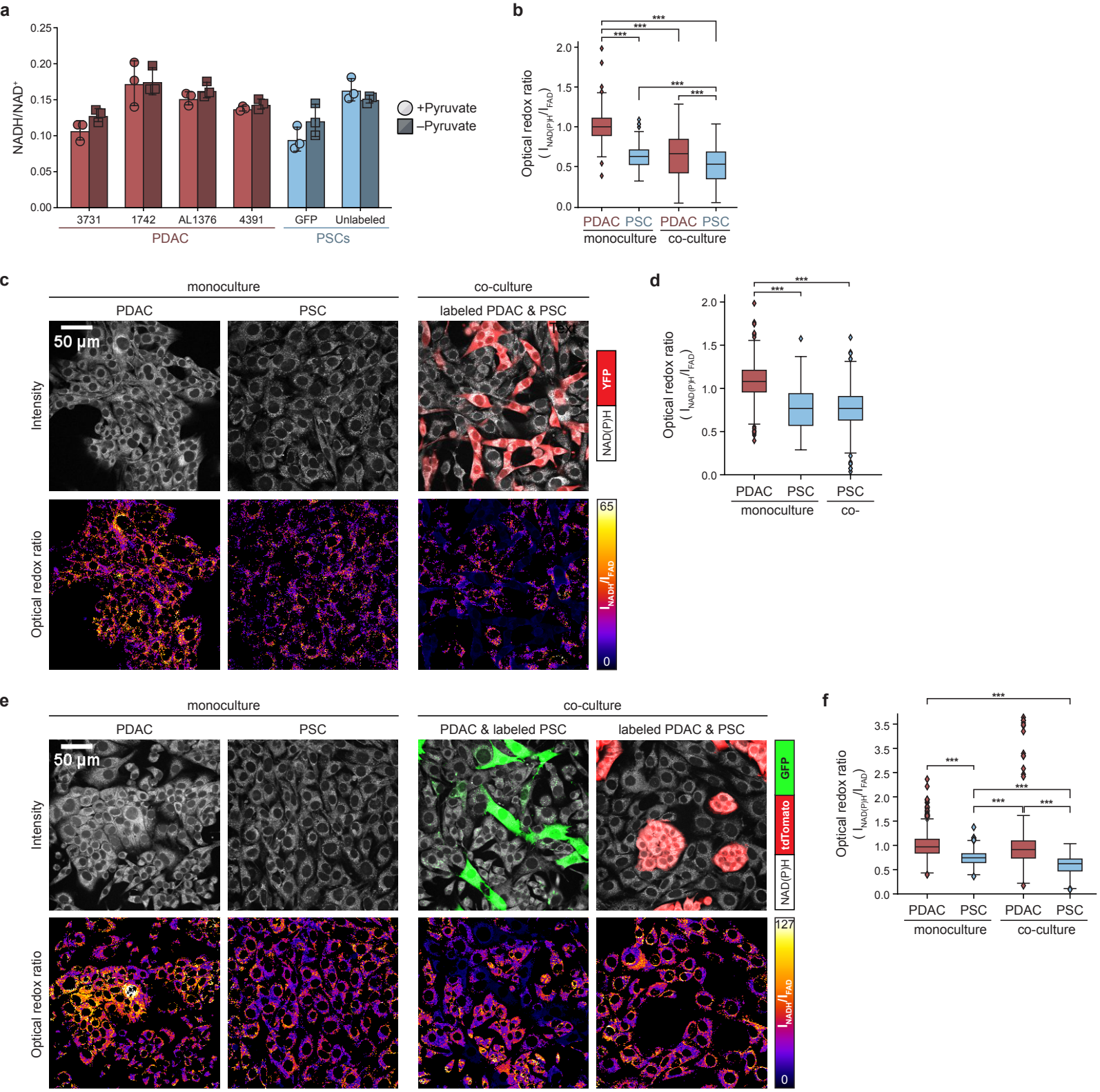
Supplementary Figure 6. LbNox expression in either PDAC cancer cells or PSCs does not affect organoid growth (a) Western blot analysis of Flag-tagged LbNox expression in PDAC cells transfected with empty vector (EV) or a doxycycline-inducible Flag-tagged LbNox construct

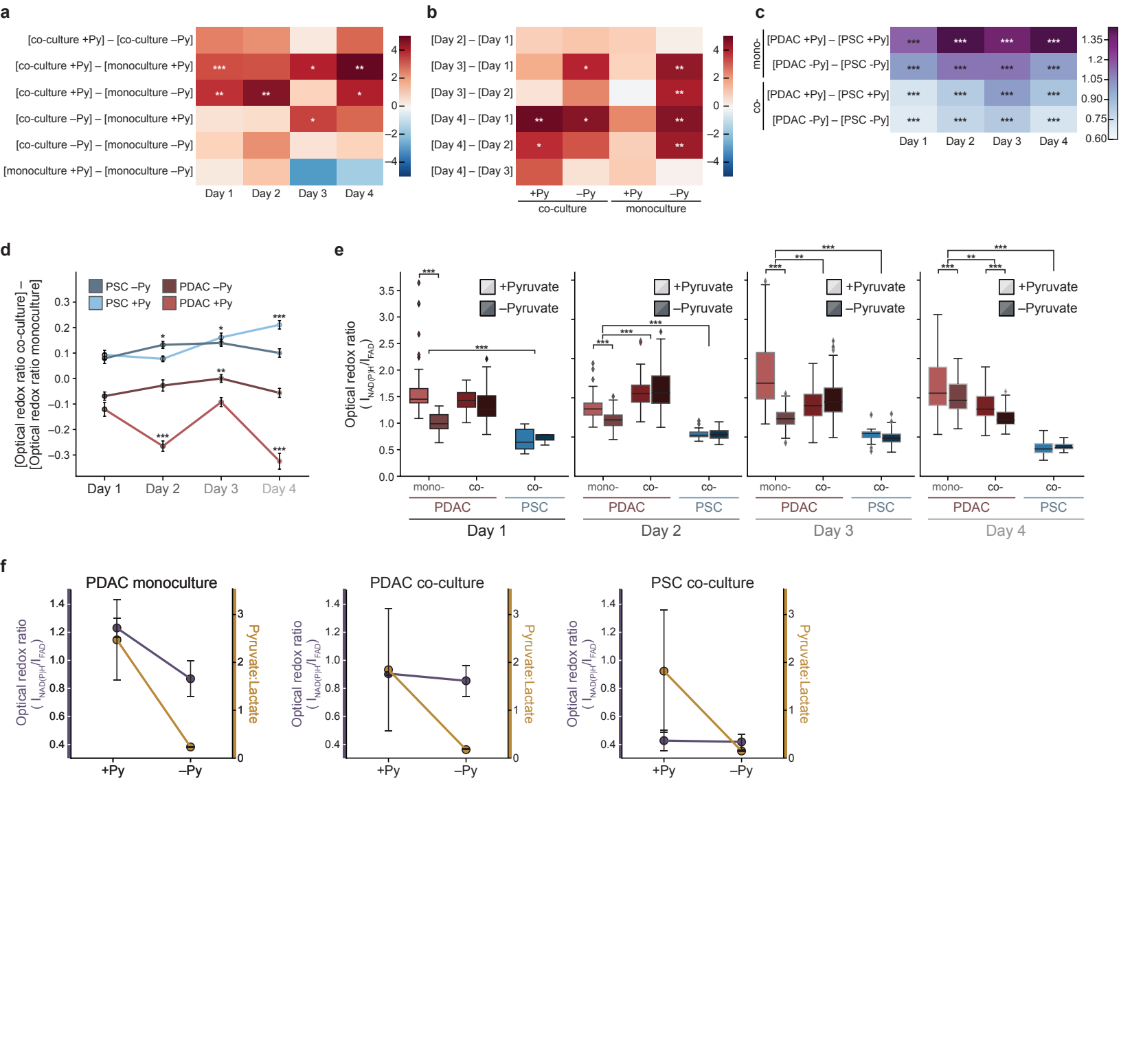
(LbNox) and exposed to the indicated concentration of doxycycline for 48 hours. Vinculin expression was also assessed as a loading control. (b) $NADH/NAD^+$ ratio of PDAC cells exposed to 1 μg/mL doxycycline for 48 hours (c) Growth of PDAC organoids was assessed by measuring TdTomato fluorescence intensity (left) or counting organoid number (middle), with mean +/- std deviation shown. Organoids were exposed to doxycycline for at least 48 hours prior to analysis to induce LbNox expression and assessed 4 days after plating in media conditions without pyruvate. Western blot analysis of Flag-tagged PDAC organoids transfected with EV or a LbNox is also shown to confirm expression in these conditions (right). (d) $NADH/NAD^+$ ratio of pancreatic stellate cells (PSCs) expressing empty vector (EV) or doxycycline-inducible Flag-tagged LbNox (LbNox) after culture with 1 μg/mL doxycycline for 48 hours prior to analysis (top); western blot analysis of Flag-tagged LbNox expression in PSCs that were transfected with EV or LbNox (below). (e) Tomato-labeled organoids were cultured either alone or with 1 μg/mL doxycycline pretreated PSCs expressing either EV or LbNox. Organoid growth after 4 days of culture in media without pyruvate as assessed by TdTomato fluorescence intensity (left) or by organoid number (right) with mean +/- std deviation shown.

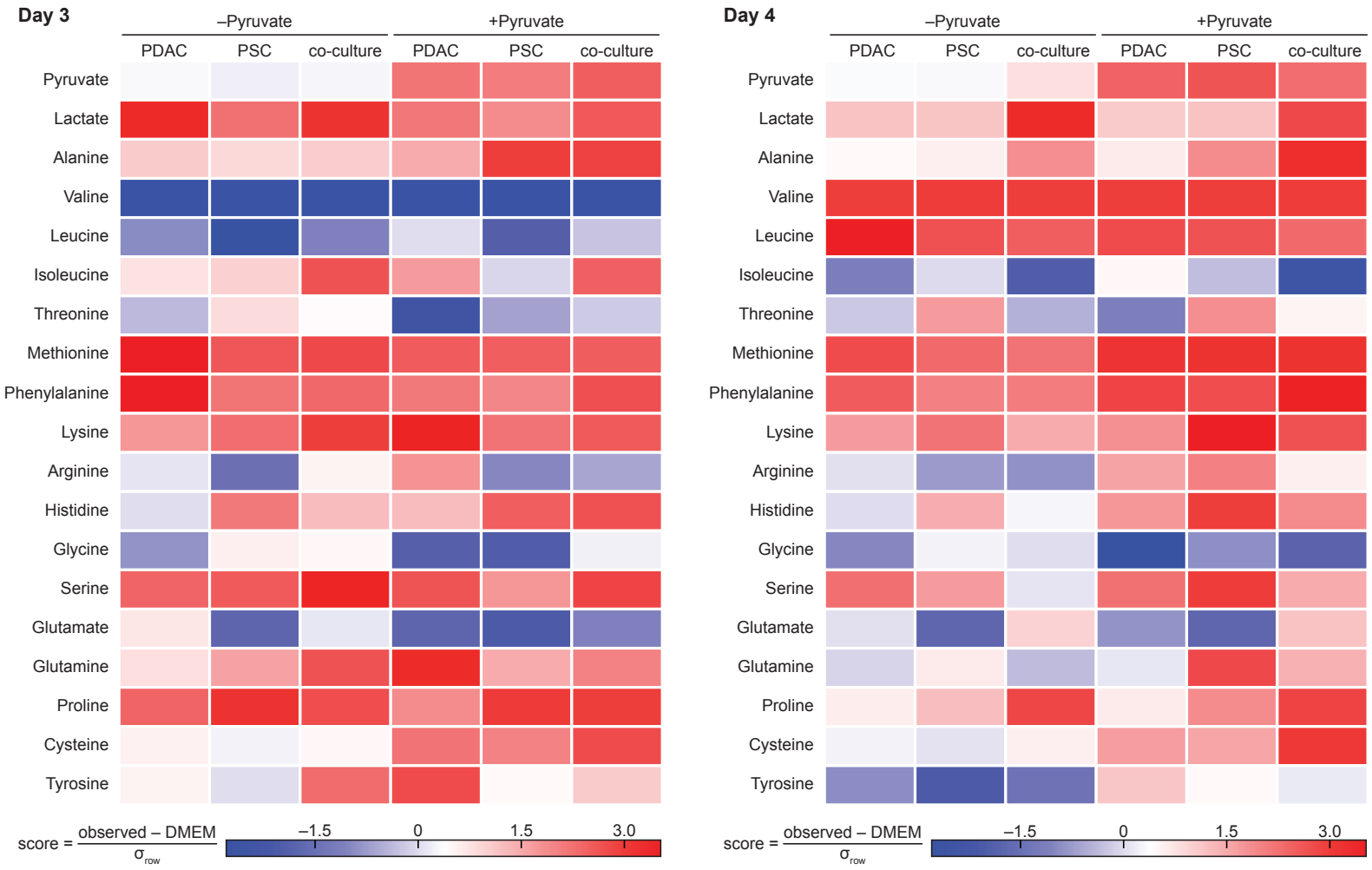
Supplementary Figure 7. Cell segmentation results for PDAC cells in 2D and 3D organoids. Representative cell segmentation results for PDAC cells cultured as 2D monolayer (top) and PDAC cells cultured as 3D organoids (bottom). (Left to Right) Representative NAD(P)H intensity images, corresponding manually segmented cell nuclei, corresponding cell boundary identified using automated Voronoi-based propagation method expanding from nuclei, and corresponding cytoplasm mask created by subtracting nuclei from cell boundary. Single cell segmentation of 2D monolayer and 3D organoid fluorescence images were performed using a customized semi-automated Cellprofiler pipeline.


Pancreatic Ductal Adenocarcinoma (PDAC)
Pancreatic stellate cells (PSC) / Mouse embryonic fibroblasts (MEF)
Matrigel
Transwell
transwell insert
media
Organoid monoculture
Alanine
/
Pyruvate
Organoid co-culture


a
[+Ala] – [control]
[+Py] – [+Ala]
[+Py] – [control]
8
4
0
–4
–8
mono-culture
+MEF
+PSC
co-culture
b
[+MEF] – [mono]
[+PSC] – [+MEF]
[+PSC] – [mono]
**
***
***
*
16
8
0
–8
–16
control
+Ala
+Py
c
Num. Organoids
25
20
15
10
5
0
**
***
control
+Ala
+Py
+MEF
+PSC
mono-
co-
d
Organoid area (a.u.)
35
30
25
20
15
10
5
0
+MEF
+PSC
Alanine:
Pyruvate:
monoculture
co-culture
e
Num. Organoids
100
80
60
40
20
***
***
***
***
***
***
**
-Py
+Py
+MEF
+PSC4
+PSC5
+primaryPSC
monoculture
co-culture
f
Organoid area (a.u.)
12
10
8
6
4
2
0
***
*
**
***
***
**
***
-Py
+Py
+MEF
+PSC4
+PSC5
+primaryPSC
monoculture
co-culture
g
Fluorescence (A.U.)
15000
10000
5000
0
PSC 5 co-culture
PSC 5 monoculture
0
1
2
3
4
5
6
Days
h
Fluorescence (A.U.)
12000
10000
8000
6000
4000
2000
0
PSC 4 co-culture
PSC 4 monoculture
0
1
2
3
4
5
6
Days


a
NADH/NAD+
0.25
0.20
0.15
0.10
0.05
0.00
3731
1742
AL1376
4391
GFP
Unlabeled
PDAC
PSCs
+Pyruvate
–Pyruvate
b
Optical redox ratio
(I NAD(P)H / I FAD)
2.0
1.5
1.0
0.5
0.0
***
PDAC PSC PDAC PSC
monoculture co-culture
c
monoculture
co-culture
PDAC
PSC
labeled PDAC & PSC
50 μm
Intensity
Optical redox ratio
YFP
NAD(P)H
65
0
I NADH / I FAD
d
Optical redox ratio
(I NAD(P)H / I FAD)
PDAC PSC PSC
monoculture co-
e
monoculture
co-culture
PDAC
PSC
PDAC & labeled PSC
labeled PDAC & PSC
50 μm
Intensity
Optical redox ratio
GFP
tdTomato
NAD(P)H
127
0
I NADH / I FAD
f
Optical redox ratio
(I NAD(P)H / I FAD)
3.5
3.5
2.5
2.0
1.5
1.0
0.5
0.0
***
PDAC PSC PDAC PSC
monoculture co-culture


a
[co-culture +Py] – [co-culture –Py]
[co-culture +Py] – [monoculture +Py]
[co-culture +Py] – [monoculture –Py]
[co-culture –Py] – [monoculture +Py]
[co-culture –Py] – [monoculture –Py]
[monoculture +Py] – [monoculture –Py]
Day 1
Day 2
Day 3
Day 4
b
[Day 2] – [Day 1]
[Day 3] – [Day 1]
[Day 3] – [Day 2]
[Day 4] – [Day 1]
[Day 4] – [Day 2]
[Day 4] – [Day 3]
+Py
–Py
+Py
–Py
co-culture
monoculture
c
mono-
co-
[PDAC +Py] – [PSC +Py]
[PDAC -Py] – [PSC -Py]
[PDAC +Py] – [PSC +Py]
[PDAC -Py] – [PSC -Py]
Day 1
Day 2
Day 3
Day 4
d
PSC –Py
PSC +Py
PDAC –Py
PDAC +Py
[Optical redox ratio co-culture] – [Optical redox ratio monoculture]
Day 1
Day 2
Day 3
Day 4
e
+Pyruvate
–Pyruvate
Optical redox ratio (I NAD(P)H / I FAD)
mono-
co-
co-
PDAC
PSC
Day 1
Day 2
Day 3
Day 4
f
PDAC monoculture
PDAC co-culture
PSC co-culture
Optical redox ratio (I NAD(P)H / I FAD)
Pyruvate:Lactate
+Py
–Py


Day 3
–Pyruvate
+Pyruvate
PDAC
PSC
co-culture
PDAC
PSC
co-culture
Pyruvate
Lactate
Alanine
Valine
Leucine
Isoleucine
Threonine
Methionine
Phenylalanine
Lysine
Arginine
Histidine
Glycine
Serine
Glutamate
Glutamine
Proline
Cysteine
Tyrosine
score = observed – DMEM / σrow
–1.5
0
1.5
3.0
Day 4
–Pyruvate
+Pyruvate
PDAC
PSC
co-culture
PDAC
PSC
co-culture
Pyruvate
Lactate
Alanine
Valine
Leucine
Isoleucine
Threonine
Methionine
Phenylalanine
Lysine
Arginine
Histidine
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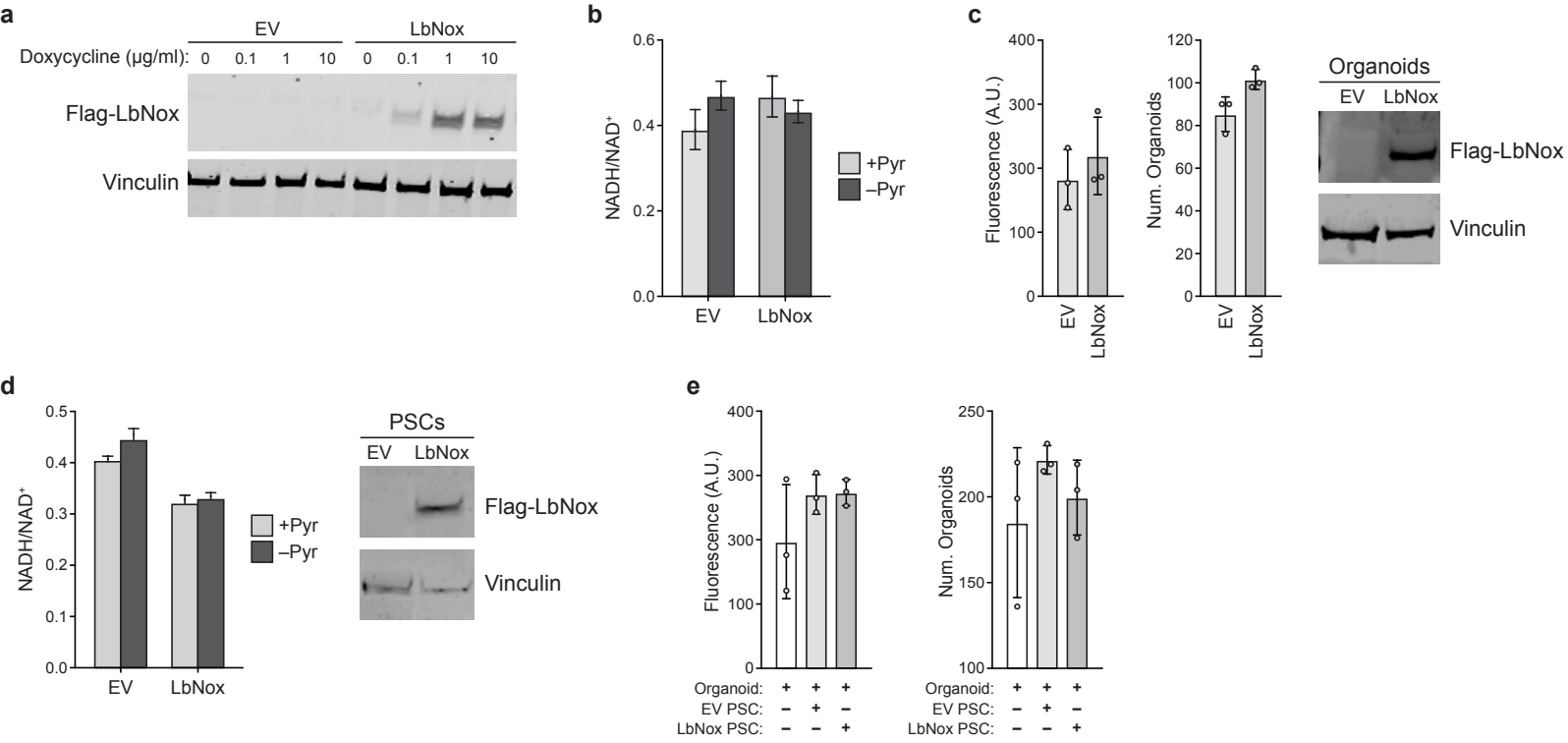
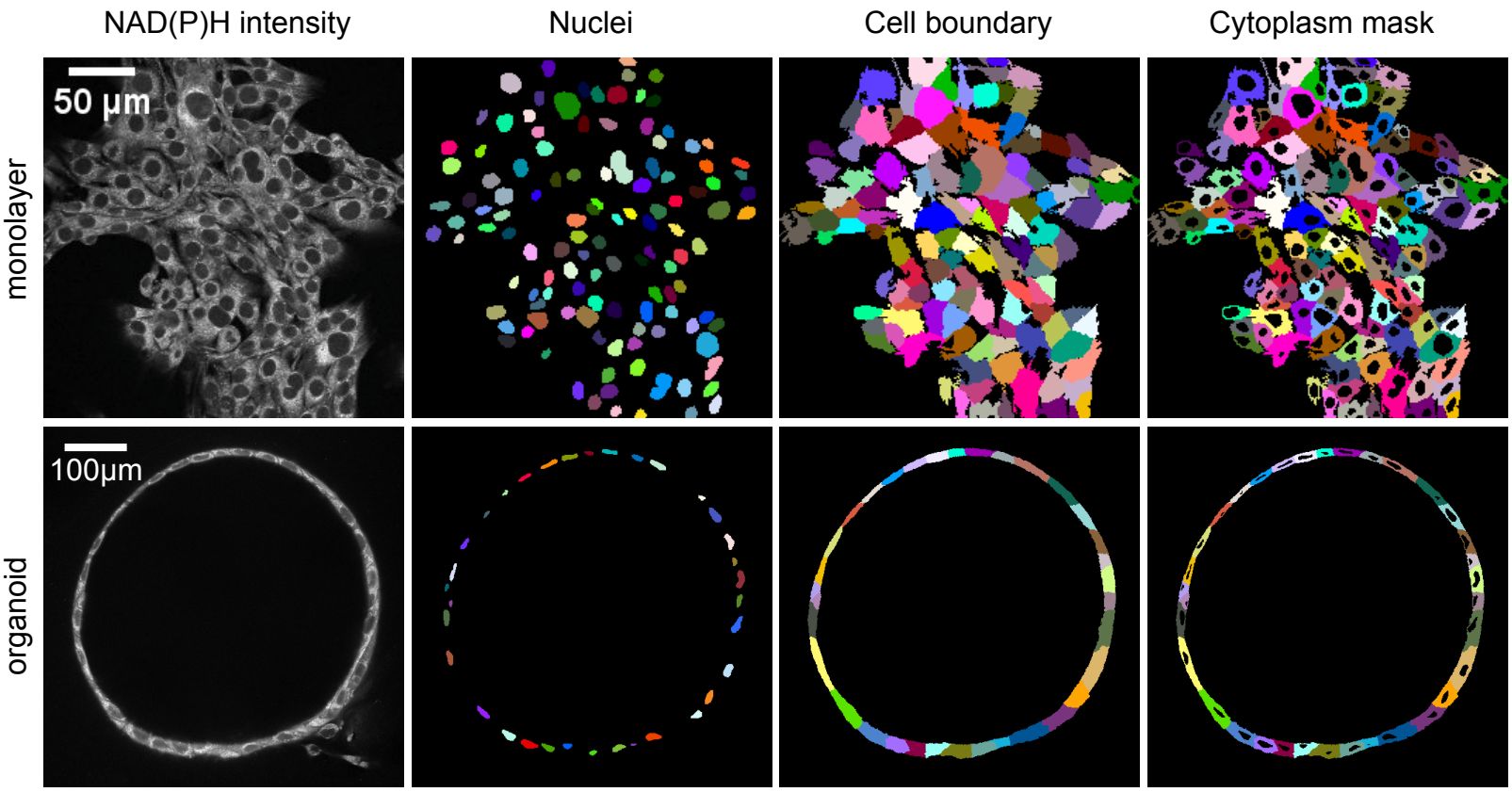
–1.5
0
1.5
3.0


a
EV
LbNox
Doxycycline (μg/ml): 0 0.1 1 10 0 0.1 1 10
Flag-LbNox
Vinculin
b
NADH/NAD+
0.6
0.4
0.2
0.0
+Pyr
–Pyr
EV
LbNox
c
Fluorescence (A.U.)
400
300
200
100
0
EV
LbNox
Num. Organoids
120
100
80
60
40
20
0
EV
LbNox
Organoids
EV LbNox
Flag-LbNox
Vinculin
d
NADH/NAD+
0.5
0.4
0.3
0.2
0.1
0.0
+Pyr
–Pyr
EV
LbNox
PSCs
EV LbNox
Flag-LbNox
Vinculin
e
Fluorescence (A.U.)
400
300
200
100
0
Organoid: + + +
EV PSC: – + –
LbNox PSC: – – +
Num. Organoids
250
200
150
100
Organoid: + + +
EV PSC: – + –
LbNox PSC: – – +


NAD(P)H intensity
Nuclei
Cell boundary
Cytoplasm mask
monolayer
organoid
50 µm
100µm

Supplementary Table 1. Number of cells segmented for data shown in Figure (3e)

Day	Cell type	Culture	Pyruvate	n = dishes	images per dish	n = number of cells
1	PDAC cells	monoculture	-	3	2	172
			+	3	2	197
		co-culture	-	3	2	246
			+	3	2	380
	PSCs	monoculture	-	3	2	57
			+	3	2	59
		co-culture	-	3	2	48
			+	3	2	71
2	PDAC cells	monoculture	-	3	2	162
			+	3	2	180
		co-culture	-	3	2	443
			+	3	2	352
	PSCs	monoculture	-	3	2	63
			+	3	2	158
		co-culture	-	3	2	78
			+	3	2	96
3	PDAC cells	monoculture	-	3	2	262
			+	3	2	228
		co-culture	-	3	2	414
			+	3	2	445
	PSCs	monoculture	-	3	2	69
			+	3	2	129
		co-culture	-	3	2	102
			+	3	2	94
4	PDAC cells	monoculture	-	3	2	355
			+	3	2	201
		co-culture	-	3	2	347
			+	3	2	258
	PSCs	monoculture	-	3	2	38
			+	3	2	104
		co-culture	-	3	2	46
			+	3	2	91

Supplementary Table 2. Number of PSCs segmented for data shown in Figure (4e)

Day	Group	Pyruvate	n= number of cells
1	non-touching	-	31
		+	11
	touching	-	48
		+	71
3	non-touching	-	21
		+	11
	touching	-	102
		+	94
4	non-touching	-	15
		+	14
	touching	-	46
		+	91

Supplementary Table 3. Total ion count of metabolites analyzed by GC-MS

Day	Culture	Pyruvate	Norvaline	Pyruvate	Lactate	Alanine	Glycine	Serine	Glutamate	Glutamine	Proline	Valine
N.A	DMEM	-	15084455	553970	740208	85201	9744334	11728719	531832	6541063	116544	15085282
3	PDAC	-	25928704	14838184	57509896	1165272	16381055	18836523	1822534	21182121	449258	25929205
	PDAC	+	28225777	132167936	39843890	1697383	16711350	21129323	842567	36310753	392329	28226069
	PSC	-	30304785	8337679	44081307	1128474	21224874	22463438	910852	29088285	673542	30305816
	PSC	+	29752079	131561645	36439368	3662781	17474396	19626044	671759	27908662	637725	29751580
	co-culture	-	25835047	12054600	54340725	1134918	17977933	21486079	1555297	30063888	502175	25835703
	co-culture	+	19261828	102802040	32756850	2305871	13184338	14899538	734556	20035413	407791	19265338
4	PDAC	-	29519435	23709566	106600392	2303452	20201055	22170598	2639685	25816088	556962	29518534
	PDAC	+	24493446	130713448	80782497	2587837	14258607	18278344	1386351	22690146	482876	24493425
	PSC	-	37660057	27196813	131944631	3654676	28659296	25577775	1278930	39367898	1324800	37660561
	PSC	+	26732729	154611673	97097792	8195615	18447596	22498863	912289	40435119	1418959	26732318
	co-culture	-	37747945	67417515	387134121	11285638	28131560	18736750	4563478	30460745	3020796	37746154
	co-culture	+	26849767	134456602	231696029	14134446	17483311	17650684	3433589	32341170	2198290	26853318

Day	Culture	Pyruvate	Leucine	Isoleusine	Threonine	Methonine	Phenylalanine	Cysteine	Lysine	Arginine	Tyrosine	Histidine
N.A	DMEM	-	17451639	24327708	1742332	3955188	7915757	38187	6541530	1748833	6635237	3162149
3	PDAC	-	28065285	38983917	4373985	7977883	16296335	421359	21161974	3246141	8140105	5007524
	PDAC	+	31350199	44227611	3545756	7348326	14087672	1182719	36501917	4744240	12003306	10124840
	PSC	-	31265899	46082955	5961841	7981287	15233064	343769	29239465	2661475	8654133	14436643
	PSC	+	31517684	42979630	4822439	7655114	14379617	1157178	27964363	2841764	9222635	15586769
	co-culture	-	27882673	42257402	4858728	7001965	13370095	385378	30068021	3533054	10381698	9283795
	co-culture	+	21223872	31227564	3331613	4992181	10542146	984187	20027536	2009568	6540074	10632281
4	PDAC	-	33086128	43619997	5238090	7782327	14915066	530172	25787038	3059186	10038087	6959363
	PDAC	+	25620083	37101841	3884501	7000963	13204257	1775342	22635984	3205926	10387066	14352934
	PSC	-	39204020	56592459	8193553	8981939	17021007	369519	39520772	3322879	11154428	19974571
	PSC	+	27790964	39964515	5909612	7713833	14072061	1818130	40424538	3712538	10655947	22681252
	co-culture	-	38650364	55171686	6471865	8724924	17314609	1193473	30472913	3258198	12304868	11507648
	co-culture	+	27185497	38903167	5204657	7748631	16508145	3504563	32313410	3059359	10349201	16686617