Supplemental Material

Supplemental Figure Legends

Supplemental Figure 1: PVR is required for antiviral defense in *Drosophila*, related to Figure 1. (A) Immunoblot quantification for phospho-ERK, total ERK, and tubulin provided for Figure 1B. Mean ± SD; n=3; *p<0.05. (B) Immunoblot quantification for PVR and tubulin provided for Figure 1C. Mean ± SD; n=3; *p<0.05. (C) Representative images of flies of the indicated genotypes fed PBS with red dye for 7 days. (D) RT-qPCR analysis of DENV RNA normalized to rp49 and shown relative to control (Myo1A>+) from the posterior half of midguts isolated from flies of the indicated genotype at 10 dpi. Mean ± SD; n=3; *p<0.05. (E-F) Representative images of the posterior midgut of Myo1A>+ (E) or Myo1A>PVR IR ^{VDRC} (F) challenged with the DCV (E) or SINV (F) at 7 dpi (10x, virus-green, nuclei-blue). (G) RT-qPCR analysis of viral RNA normalized to rp49 and shown relative to control (HS>+) from midguts isolated from flies of the indicated genotypes at 7 dpi. Mean ± SD; n≥3; *p<0.05. (H) Immunoblot quantification for phospho-ERK and total ERK provided for Figure 1G. Mean ± SD; n=3; *p<0.05.

Supplemental Figure 2: Pvf2 is required for antiviral defense in *Drosophila* and overexpression of Pvf2 is protective against enteric infections, related to Figure 2. (A) RT-qPCR analysis of viral RNA normalized to rp49 and shown relative to control (w^{1118}) from midguts isolated from flies of the indicated genotypes at 7 dpi. Mean ± SD; n=3; *p<0.05. (B) Immunoblot quantification for phospho-ERK, total ERK, and tubulin provided for Figure 2E, Mean ± SD; n=3 (phospho-ERK, total ERK); n=2 (tubulin); *p<0.05. (C) Representative immunoblot analysis of 20 pooled HS>+ or HS>Pvf2 intestines. (D) Immunoblot quantification for phospho-ERK and total ERK provided for Supplemental Figure 2C. Mean ±SD; n=3; *p<0.05. (E) Representative immunoblot of 20 pooled Myo1A>+ or Myo1A>Pvf2 intestines. (F) Immunoblot quantification for phospho-ERK and total ERK for Supplemental Figure 2E. Mean ± SD; n=3; *p<0.05. (G) RT-qPCR analysis of viral RNA normalized to rp49 and shown relative to control (Myo1A>+) from midguts isolated from flies of the indicated genotypes at 7 dpi. Mean ± SD; n=4; *p<0.05.

Supplemental Figure 3: Validation of antibiotic-treated and germ-free flies, related to Figure 4. (A) *Drosophila* cells were treated for 1h with the supernatant of the indicated bacterial species and diptericin expression was monitored by RT-qPCR for three independent experiments with mean ± SD shown for n=3. (B, D) Representative images of bacterial plates from 5 pooled guts from antibiotic treated (B) or germ-free (D) and control animals. (C, E) Representative images of flies from antibiotic-treated (C) or germ-free (E) and controls fed PBS with red dye for 7 days. (F) Immunoblot quantification for phospho-ERK and total ERK provided for Figure 4D. Mean ± SD; n=3; *p<0.05.

Supplemental Figure 4: NF-kB, not JNK, is required for antiviral defense, related to Figure 6. (A) Representative images of midguts from sibling control or Rel mutant flies 7 dpi (40x; DCV-green, nuclei-blue). (B-D) RT-qPCR analysis of DCV RNA normalized to rp49 and shown relative to control from midguts isolated from flies of the indicated genotypes at 7 dpi. Mean ± SD; n≥3; *p<0.05. (E) RT-qPCR analysis of DCV RNA normalized to rp49 and shown relative to control (Tak1 -/+ abx-) from midguts isolated

from of flies the indicated genotypes at 7 dpi. Mean ± SD; n=4. (F) RT-qPCR analysis of Pvf2 RNA normalized to rp49 and shown relative to control (Myo1A>+) from midguts isolated from flies of the indicated genotypes at 4 hpi. Mean ± SD; n=3; *p<0.05.

Supplemental Figure 5: Antiviral ERK activation requires a two-signal system, related to Figure 7. (A) RT-qPCR analysis of viral RNA normalized to rp49 and shown relative to control (HS>+) from midguts isolated from flies of the indicated genotypes at 7 dpi. Mean ± SD; n=3; *p<0.05. (B) In posterior midgut enterocytes, Pvf2 induction requires two-signals to activate antiviral ERK signaling. Gram-negative commensals, such as *A. pomorum*, through recognition by PGRP-LC activate the Imd pathway, converging on NF-kB (Signal 1). However, NF-kB activation is not sufficient to induce Pvf2. A virus-dependent Cdk9-dependent signal is also required for Pvf2 induction (Signal 2). Both signals are necessary for antiviral ERK signaling in the intestine. It is unknown if Pvf2-PVR signaling is acting by an autocrine or paracrine mechanism to activate the antiviral ERK pathway.

Supplemental Table 1: Drosophila stocks used, related to Experimental Procedures.

Supplemental Table 2: Primers used, related to Experimental Procedures.

Table S1. *Drosophila* Stocks, related to Experimental Procedures

Stock	Donor	References
Heat Shock-GAL4	Bloomington Stock Center (FBst0001799)	
UAS-EGFR DN	Bloomington Stock Center (FBst0005364)	(Buchon et al., 2010; Buff et al., 1998; Molnar and de Celis, 2013; Wahlstrom et al., 2006)
UAS-Pvf2 ($Pvf2^{d02444}$)	Bloomington Stock Center (FBst0019631)	(Cho et al., 2002; Choi et al., 2008; Munier et al., 2002)
$Pvf2^{c06947}$	Bloomington Stock Center (FBst0020361)	(Cho et al., 2002; Choi et al., 2008; Munier et al., 2002; Wood et al., 2006)
Pvf2-lacZ	M.A. Yoo (Pusan National University, Busan, South Korea) (FBtp0052107)	(Bond and Foley, 2009; Choi et al., 2008)
Myo1A-GAL4	E. Baehrecke (University of Massachusetts Medical School, Worcester, MA)	(Jiang et al., 2009; Morgan et al., 1994; Xu et al., 2013)
UAS-PVR IR^{8222R} NIG	B. Stronach (University of Pittsburgh, Pittsburgh, PA) (FBal0275906)	(Brock et al., 2012; Ishimaru et al., 2004; Tran et al., 2013; Wu et al., 2009)
UAS-PVR $IR^{KK101575}$ VDRC	B. Stronach (University of Pittsburgh, Pittsburgh, PA) (FBst0477180)	(Tran et al., 2013)
UAS-bsk DN	B. Stronach (University of Pittsburgh, Pittsburgh, PA) (FBst0006409)	(Adachi-Yamada et al., 1999)
Rel^{E38}	N. Silverman (University of Massachusetts Medical School,	(Hedengren et al., 1999; Park et al., 2004; Takehana

	Worcester, MA) (FBst0009458)	et al., 2002)
$Tak1^{2}$	N. Silverman (University of Massachusetts Medical School, Worcester, MA) (FBst0026272)	(Delaney et al., 2006; Stronach et al., 2014; Vidal et al., 2001)
Imd^{1}	N. Silverman (University of Massachusetts Medical School, Worcester, MA) (FBal0045906)	(Lemaitre et al., 1995; Lemaitre et al., 1996)
UAS-IMD	N. Buchon (Cornell University, Ithaca, NY)(FBal0138219)	(Georgel et al., 2001)
dMyD88 $^{EP(2)2133}$	N. Silverman (University of Massachusetts Medical School, Worcester, MA) (FBal0130899)	(Nakamoto et al., 2012; Tauszig-Delamasure et al., 2002)
$Pvf1^{EP1624}$	Bloomington Stock Center (FBst0011450)	(Duchek et al., 2001)
PGRP-$LC^{\Delta E}$	N. Silverman (University of Massachusetts Medical School, Worcester, MA) (FBst0055713)	(Gottar et al., 2002; Kaneko et al., 2006; Leulier et al., 2003)
PGRP-LE^{112}	N. Silverman (University of Massachusetts Medical School, Worcester, MA) (FBst0033055)	(Aggarwal et al., 2008; Kaneko et al., 2006; Takehana et al., 2002)
PGRP-LE^{112}; PGRP-$LC^{\Delta E}$	N. Silverman (University of Massachusetts Medical School, Worcester, MA)	(Aggarwal et al., 2008; Takehana et al., 2002)
UAS-Cdk9 $IR^{KK101197}$	Vienna Drosophila Resource Center (FBst0475419)	(Xu et al., 2012)

Table S2. Quantitative Real-Time PCR primers, related to Experimental Procedures

Primer Name	Sequence
rp49 Forward	AAG AAG CGC ACC AAG CAC TTC ATC
rp49 Reverse	TCT GTT GTC GAT ACC CTT GGG CTT
DCV Forward	TGG GAC AGG CAG TTA ATT CGT CCA
DCV Reverse	AAG ACC GCA GTG TCT ACA CCA CAT
SINV Forward	GCT GAA ACA CCA TCG CTC TGC TTT
SINV Reverse	TGG TGT CGA AGC CAA TCC ACT ACA
VSV Forward	CGG AGG ATT GAC GAC TAA TGC
VSV Reverse	ACC ATC CGA GCC ATT CGA
DENV-2 Forward	TGA GGA CTA CAT GGG CTC TG
DENV-2 Reverse	AAA CCT CCC TGG ATT TCC TT
Pvf1 Forward	TGG AGC AGG CCG AGA ACA AGT ATT
Pvf1 Reverse	CCT GGA CAA TGA AGC GTT TGC GAT
Pvf2 Forward	ACA ATT CTG CAC AGA TGC AGC GAC
Pvf2 Reverse	CAT TGG AAC GGC CAT CCA CTT TGT
Pvf3 Forward	TGC CTC GGT GGT CAT TAG GTT CTT
Pvf3 Reverse	GCA GCA TCA CTT GCG TCA TCA CAA
dipt Forward	GAC TGG CTT GTG CCT TC
dipt Reverse	CCT GAA GGT ATA CAC TCC

Supplemental Methods

Fly Rearing and Infections. U0126 (500 μM) was used as described (Bangi et al., 2011; Xu et al., 2013; Zhang et al., 2011).

To generate germ-free flies, eggs were washed in sterile deionized water, immersed in 50% sodium hypochlorite solution for 2 minutes, and rinsed three times in sterile water. For conventionally reared sibling controls, the eggs were immersed in sterile water as opposed to sodium hypochlorite (Ridley et al., 2012). Embryos were transferred to axenic standard fly food vials (2% yeast, 6.97% cornmeal, 9.6% sucrose, 1.5% agar) (Shin et al., 2011). Germ-free and conventional flies were aged to 7-10 days old and infected as above.

For antibiotic experiments, four to seven day old female flies were transferred onto vials containing 200 μl of agarose- food (1.5% agarose, 7% corn syrup, 2% Bacto TC Yeastolate) supplemented with doxycycline (640 μg/ml), ampicillin (640 μg/ml), and kanamycin (1 mg/ml). Control flies were reared on agarose-food supplemented with vehicle. Three days later, flies were transferred to whatman paper containing 10 μl of virus for one day and transferred onto fresh antibiotic- or vehicle-containing food every 3 days for the duration of the experiment.

Mono-associated flies were established by antibiotic treating and then transferring onto fly food amended with 5 x 10^8 CFU of the indicated bacterial strains for 3 days. Oral infections were performed as described above. Commensals were heat killed by incubating at 80°C for 1 hour.

Cell Culture. Amplicons used are described at http://flyrnai.org. dsRNA were generated and used for RNAi for 3 days as previously described (Cherry et al., 2005). In brief, cells were passaged into serum-free media (SFM) and plated into wells containing dsRNA at 250 ng/16,500 cells in 384-well plates. After 1 hour in SFM, complete media was added and cells were incubated at 25°C for 3 days for gene knockdown and infected. VSV and DCV-infected cells were processed at 24 hours after infection and SINV-infected cells were processed at 36 hours after infection (Xu et al., 2013). Automated microscopy was performed using an ImageXpress Micro and image analysis was performed as previously described (Yasunaga et al., 2014).

X-Gal Staining. X-gal staining was performed as previously described (Choi et al., 2008). In brief, 5 guts per experiment were dissected in PBS and fixed in 1% glutaraldehyde for 10 minutes. Samples were washed 3 times in PBS and stained with 0.2% X-gal in staining buffer (6.1 mM $K_4Fe(CN)_6$, 6.1 mM $K_3Fe(CN)_6$, 1 mM $MgCl_2$, 150 mM NaCl, 10 mM Na_2HPO_4, 10 mM NaH_2PO_4) in the dark at room temperature.

Immunoblotting. Immunoblot experiments probing for total ERK display only one band in *Drosophila* cell culture in contrast to two observed *in vivo* (Friedman and Perrimon, 2006; Xu et al., 2013).

Chemicals and Reagents. An antibody against DENV E protein (4G2) was provided by Michael Diamond (Washington University in St. Louis) and an antibody against PVR was provided by Katja Bruckner (University of California, San Francisco) (Sopko et al., 2015). Total Erk antibody (#9102) and phospho-Erk antibody (#4370) were obtained from Cell Signaling. Anti-DCV capsid antibody was used as described (Cherry and Perrimon,

2004). Additional chemicals and anti-tubulin antibody (T6199) were from Sigma. Commensals were grown in MRS broth in a shaking incubator at 29°C (Newell and Douglas, 2014) and *E. coli* was grown in LB broth in a shaking incubator at 37°C.

Analysis of Intestinal Integrity. Dye-feeding assays to assess intestinal barrier function were performed as previously described (Rera et al., 2011). Briefly, flies were fed food supplemented with red food dye (2.5%; FD&C red dye #40) for 7 days and monitored daily.

Bacterial Plating. Five guts per sample were dissected under sterile conditions in PBS and crushed. Serial dilutions were plated on MRS agar plates and incubated at 29°C. Three independent experiments were performed.

Supplemental References

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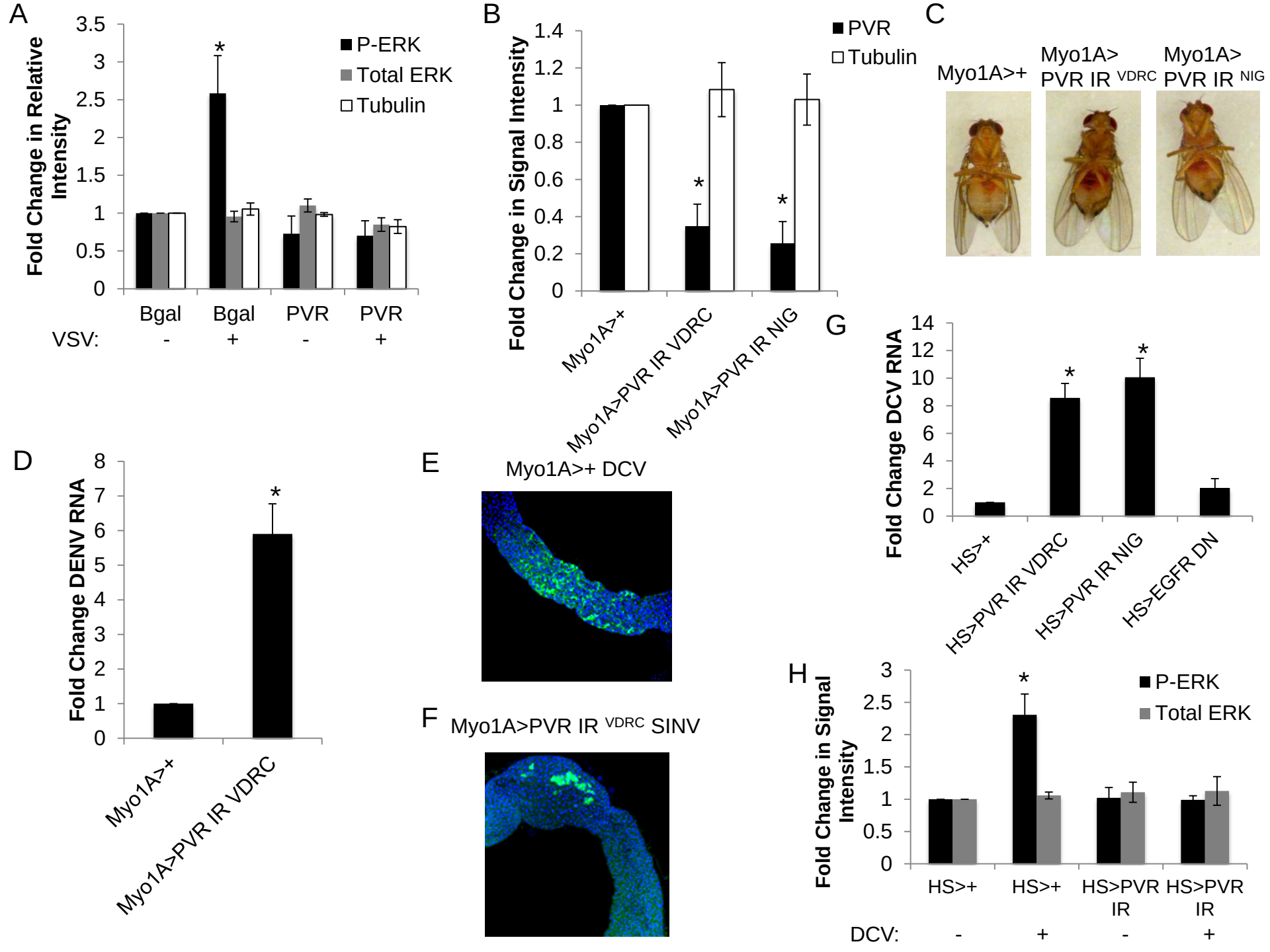
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PVR
VSV:
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Fold Change in Signal Intensity
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0.6
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PVR
Tubulin
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Myo1A>+
Myo1A>PVR IR VDRC
Myo1A>PVR IR NIG
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Myo1A> PVR IR VDRC
Myo1A> PVR IR NIG
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Myo1A>+
Myo1A>PVR IR VDRC
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Myo1A>+ DCV
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Fold Change DCV RNA
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12
10
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6
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HS>+
HS>PVR IR VDRC
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HS>EGFR DN
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Fold Change in Signal Intensity
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-
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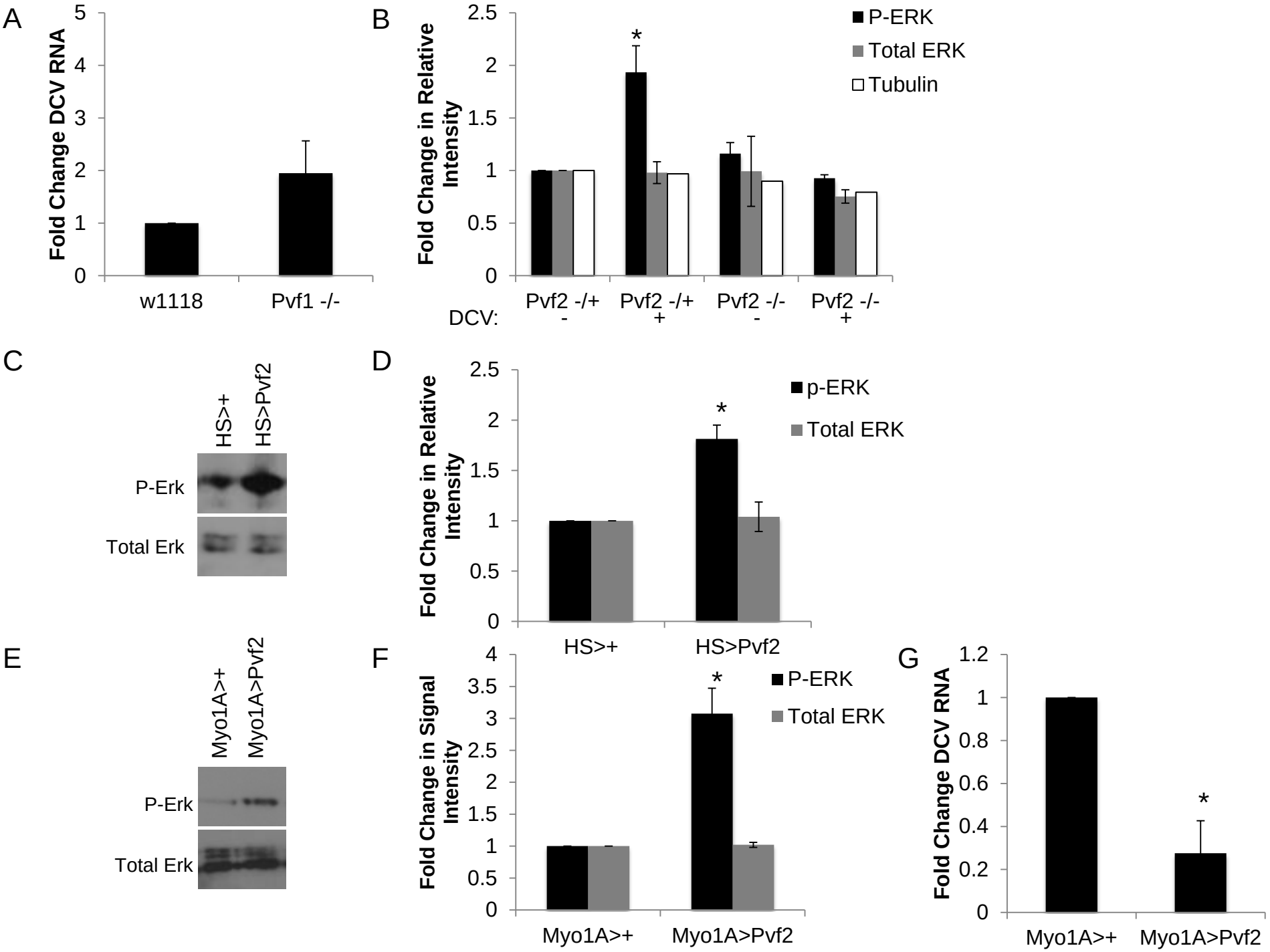
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Total ERK
Tubulin
Pvf2 -/+
-
Pvf2 -/+
+
Pvf2 -/-
-
Pvf2 -/-
+
DCV:
C
HS>+
HS>Pvf2
P-Erk
Total Erk
D
Fold Change in Relative Intensity
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1.5
1
0.5
0
*
p-ERK
Total ERK
HS>+
HS>Pvf2
E
Myo1A>+
Myo1A>Pvf2
P-Erk
Total Erk
F
Fold Change in Signal Intensity
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1.5
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0
*
P-ERK
Total ERK
Myo1A>+
Myo1A>Pvf2
G
Fold Change DCV RNA
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1
0.8
0.6
0.4
0.2
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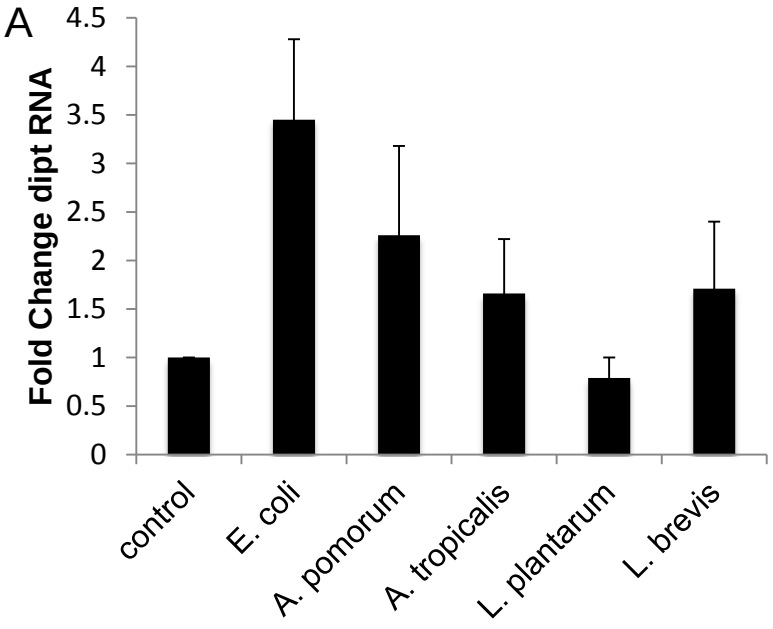
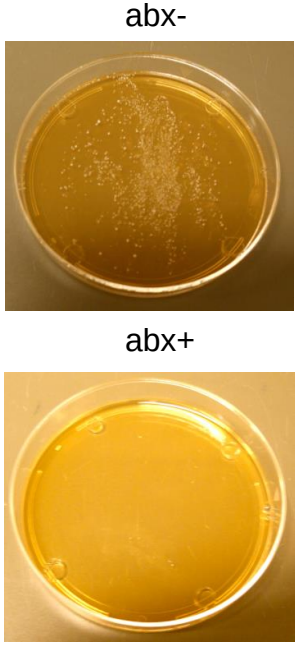
*
Myo1A>+
Myo1A>Pvf2

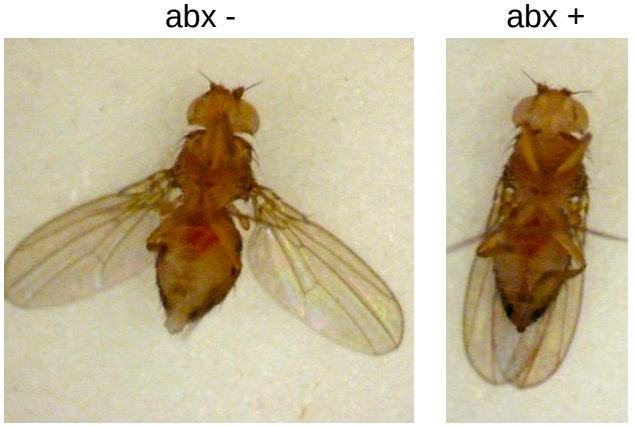
A


Fold Change dipt RNA
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
control
E. coli
A. pomorum
A. tropicalis
L. plantarum
L. brevis

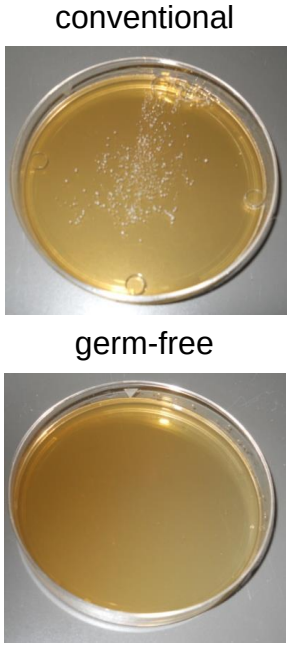
B


abx-
abx+

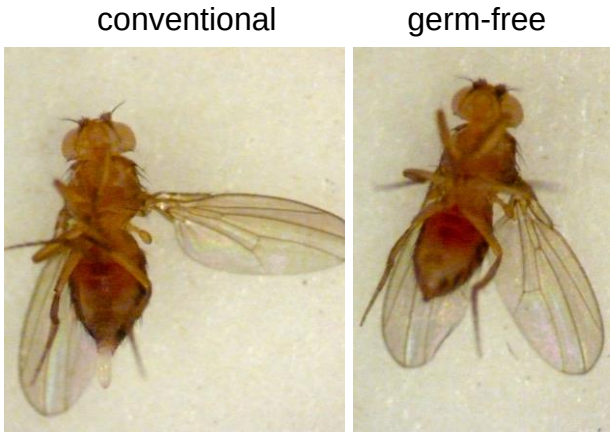
C


abx -
abx +

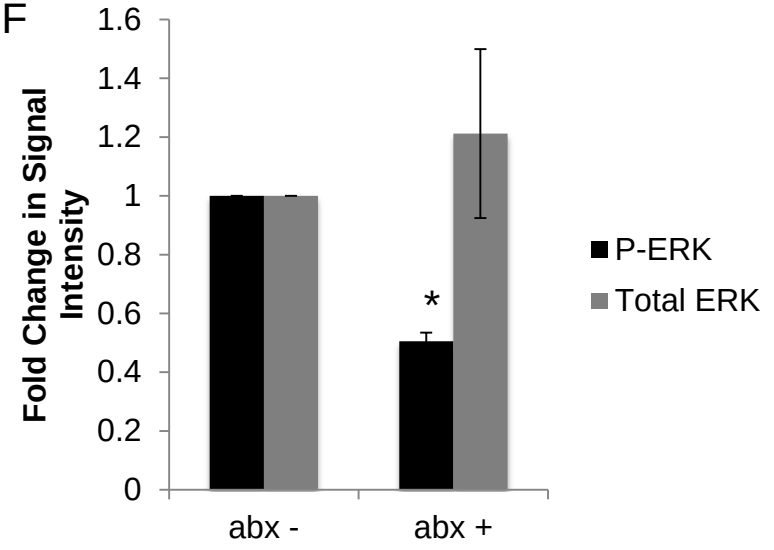
D

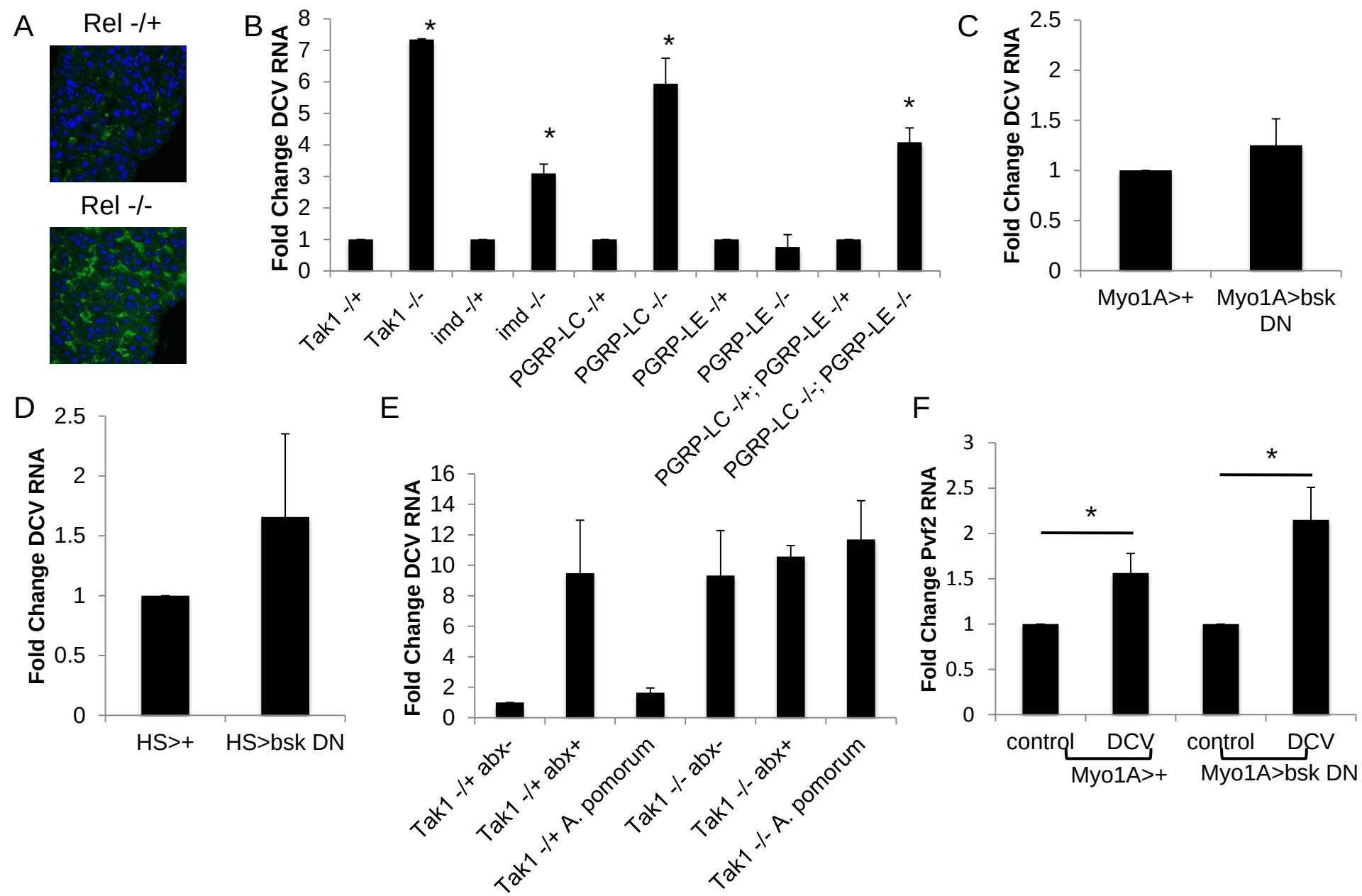

conventional
germ-free

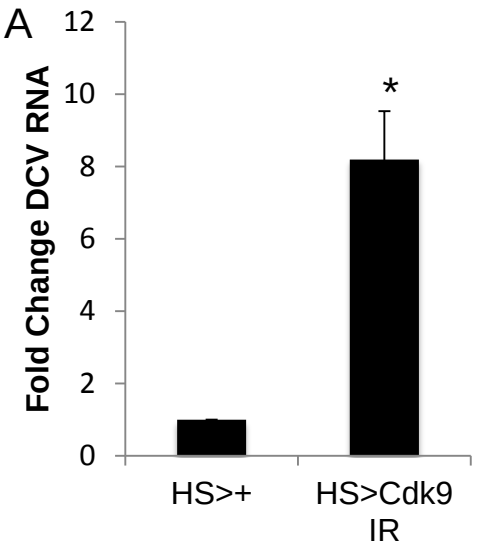
E

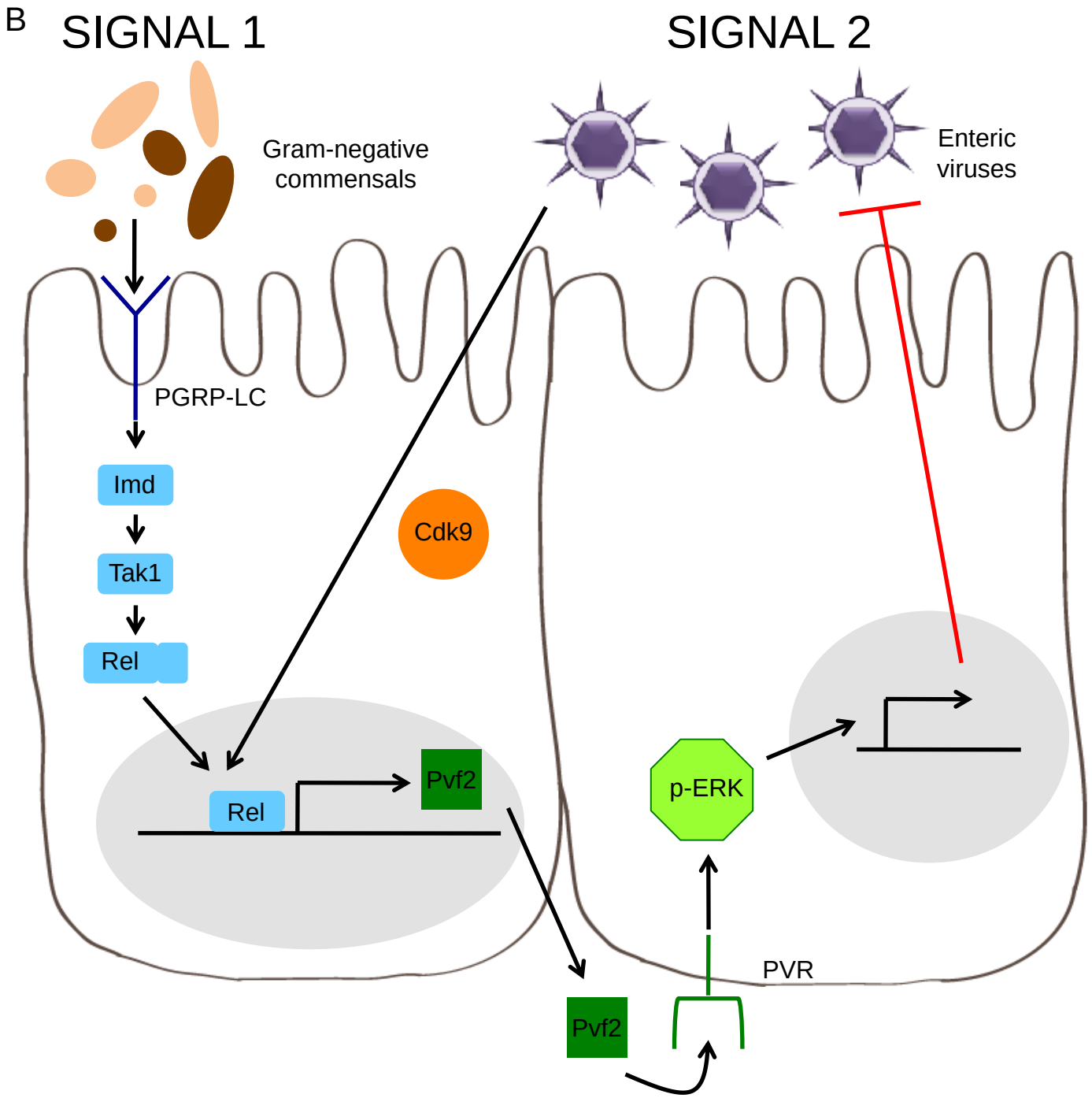

conventional
germ-free

F


Fold Change in Signal Intensity
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
*
abx -
abx +
P-ERK
Total ERK


A
Rel -/+
Rel -/-
B
Fold Change DCV RNA
0
1
2
3
4
5
6
7
8
*
*
*
Tak1 -/+
Tak1 -/-
imd -/+
imd -/-
PGRP-LC -/+
PGRP-LC -/-
PGRP-LE -/+
PGRP-LE -/-
PGRP-LC -/+; PGRP-LE -/+
PGRP-LC -/-; PGRP-LE -/-
C
Fold Change DCV RNA
0
0.5
1
1.5
2
2.5
Myo1A>+
Myo1A>bsk DN
D
Fold Change DCV RNA
0
0.5
1
1.5
2
2.5
HS>+
HS>bsk DN
E
Fold Change DCV RNA
0
2
4
6
8
10
12
14
16
Tak1 -/+ abx-
Tak1 -/+ abx+
Tak1 -/+ A. pomorum
Tak1 -/- abx-
Tak1 -/- abx+
Tak1 -/- A. pomorum
F
Fold Change Pvf2 RNA
0
0.5
1
1.5
2
2.5
3
*
*
control
DCV
control
DCV
Myo1A>+
Myo1A>bsk DN


A
Fold Change DCV RNA
12
10
8
6
4
2
0
*
HS>+
HS>Cdk9 IR


B
SIGNAL 1
SIGNAL 2
Gram-negative commensals
Enteric viruses
PGRP-LC
Imd
Tak1
Rel
Cdk9
Rel
Pvf2
p-ERK
PVR
Pvf2