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Supplementary Discussion

Our study brings to light a basic distinction in how EGFs and Upd cytokines are deployed for steady-state turnover versus injury repair. During steady-state turnover, apoptotic induction of *rho* is strictly cell autonomous (Fig. 4d-f) because E-cad-dependent activation of p120 and Arm is confined to the dying enterocyte. Of note, neither physiological apoptosis nor *E-cad* depletion activates *upd* cytokines, including the cardinal injury signal, *upd3* (Extended Data Fig. 6a-d, l). Autonomous induction of *rho* and consequent release of EGFs by the apoptotic cell confines mitogenic signaling to the precise time and place that division is needed, as appropriate for zero-sum cell replacement.

By contrast, others have shown that tissue-wide injury invokes a separate, non-cell autonomous pathway: Upon pan-enterocyte death or pathogenic infection, damaged enterocytes upregulate *upd3*, and Upd3 in turn activates enteroblasts and visceral muscle to upregulate *rho* and *EGFs*[15,16,20,21]. This non-autonomous relay causes EGFs to be released in a widespread, indiscriminate manner, as appropriate for an emergency response.

Underscoring these distinctions, enterocyte *upd3* is required for repair[6,16,20,21] but not homeostasis (Extended Data Figs. 6a-d, k and 7i), whereas enterocyte *rho* is required for homeostasis (Fig. 4k, Extended Data Fig. 8) but not repair[16]. These contrasts imply that dying cells signal differently in injury and steady-state contexts, possibly reflecting loss of the intestinal barrier or inefficient clearance of cell corpses following extensive damage. Thus, steady-state turnover is not the repair of one-cell 'mini-wounds', but rather an independent, parallel mechanism.

Supplementary Table 1 | Experimental genotypes in each figure

Figure	Panels	Genotype
Figure 1	Fig. 1a-e	w; esgGAL4, tubGAL80ts, UAS-GFP; UAS-flp, act<CD2<GAL4
	Fig. 1g-i	hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-his2A:RFP
		hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-p35
	Fig. 1j-k	w; mexGAL4, tubGAL80ts; UAS-his2A:RFP
		w; mexGAL4, tubGAL80ts; UAS-p35
		w; mexGAL4, tubGAL80ts; UAS-diap1
Figure 2	Fig. 2a	y, w; shg[mTomato]
	Fig. 2b-g	hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-his2A:RFP
		hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-p35
		hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-p35, UAS-E-cad RNAi
		hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-E-cad
		hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-E-cad RNAi
	Fig. 2h-j	w; mexGAL4, tubGAL80ts; UAS-his2A:RFP
		w; mexGAL4, tubGAL80ts; UAS-p35, UAS-E-cad RNAi
		w; mexGAL4, tubGAL80ts; UAS-p35
		w; mexGAL4, tubGAL80ts; UAS-E-cad RNAi
		w; mexGAL4, tubGAL80ts; UAS-p35, UAS-ed RNAi
	Fig. 2k	hsflp; X-15-29, tubGAL80ts/X-15-33, esgGAL4; UAS-his2A:RFP
		hsflp; X-15-29, tubGAL80ts/X-15-33, esgGAL4; UAS-E-cad
		hsflp; X-15-29, tubGAL80ts/X-15-33, esgGAL4; UAS-E-cad RNAi
Figure 3	Fig. 3a, g	w; mexGAL4, tubGAL80ts; UAS- his2A:RFP
	Fig. 3b-e	w; mexGAL4, tubGAL80ts; UAS-E-cad
		w; mexGAL4, tubGAL80ts; UAS-E-cad RNAi
		w; $Egfr^{tsla}/Egfr^{f24}$; mexGAL4 TM2/tubGAL80ts, UAS-E-cad RNAi
	Fig. 3f	hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4; UAS-p35, UAS-E-cad RNAi
	Fig. 3g	w; mexGAL4, tubGAL80ts; UAS-p35, UAS-E-cad RNAi
		w; mexGAL4, tubGAL80ts; UAS-p35
		w; mexGAL4, tubGAL80ts; UAS-p35, UAS-E-cad RNAi, UAS-spi RNAi
		w; mexGAL4, tubGAL80ts; UAS-p35, UAS-E-cad RNAi, UAS-krn RNAi
		w; mexGAL4, tubGAL80ts, UAS-spi RNAi; UAS-p35, UAS-E-cad RNAi, UAS-krn RNAi
	Fig. 3i-k	w UAS-CD8:GFP hsflp; tubGAL4/UAS-E-cad RNAi; FRT82 tubGAL80/FRT82
		w UAS-CD8:GFP hsflp; tubGAL4; FRT82 tubGAL80/FRT82
Figure 4	Fig. 4a	w; mexGAL4, tubGAL80ts; UAS-CD4:GFP (qPCR reference)
		w; mexGAL4, tubGAL80ts; UAS-E-cad
	Fig. 4a-b	w; mexGAL4, tubGAL80ts; UAS-E-cad RNAi
	Fig. 4c	w; mexGAL4, tubGAL80ts; UAS-E-cad RNAi, UAS-rho RNAi
	Fig. 4d-f	rho^{X81} (rho-lacZ)
	Fig. 4g-k	w; mexGAL4, tubGAL80ts; UAS- his2A:RFP
		w; mexGAL4, tubGAL80ts; UAS-p35
		w; mexGAL4, tubGAL80ts; UAS-p35, UAS-E-cad RNAi
		w; mexGAL4, tubGAL80ts; UAS-p35, UAS-E-cad RNAi, rho RNAi
	Fig. 4k	w; mexGAL4, tubGAL80ts, UAS-rho; UAS-p35

Supplementary Table 1 (continued) | Experimental genotypes in each figure

Figure	Panels	Genotype
Figure 4	Fig. 4k	*w; mexGAL4, tubGAL80ts;* UAS-*p35*, UAS-*E-cad* RNAi, UAS-*arm* RNAi
(continued)		*w; mexGAL4, tubGAL80ts;* UAS-*p35*, UAS-*E-cad* RNAi, UAS-*p120* RNAi
		w; mexGAL4, tubGAL80ts, UAS-*arm* RNAi*;* UAS-*p35*, UAS-*E-cad* RNAi, UAS-*p120* RNAi
		UAS-*arm*^{S10}*; mexGAL4, tubGAL80ts;* UAS-*p35*
		w; mexGAL4, tubGAL80ts; UAS-*p35*, UAS-*p120*
		UAS-*arm*^{S10}*; mexGAL4, tubGAL80ts;* UAS-*p35*, UAS-*p120*
ED Figure 1	ED Fig. 1f-g	*w; esgGAL4, tubGAL80ts,* UAS-*GFP;* UAS-*flp, act<CD2<GAL4*
ED Figure 2	ED Fig. 2b	*hsflp; X-15-29, tubGAL80ts/X-15-33, mexGAL4;* UAS-*his2A:RFP*
ED Figure 3	ED Fig. 3a	See corresponding "Total Cells (R4ab)" panels – Figs. 1k, 2h, 3g, 4k
	ED Fig. 3b	See corresponding "dpErk" panels – Figs. 3, 4, Extended Data Fig. 7
ED Figure 4	ED Fig. 4a-j	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP*
		w; mexGAL4, tubGAL80ts; UAS-*p35*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi
ED Figure 5	ED Fig. 5a-c	*w* UAS-*CD8:GFP hsflp; tubGAL4; FRT82 tubGAL80/FRT82*
		w UAS-*CD8:GFP hsflp; tubGAL4/*UAS-*E-cad* RNAi*; FRT82 tubGAL80/FRT82*
	ED Fig. 5d-f	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi
ED Figure 6	ED Fig. 6a	*w; mexGAL4, tubGAL80ts;* UAS-*CD4:GFP* (qPCR reference)
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi
	ED Fig. 6b-d	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP, upd3.1-lacZ*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, *upd3.1-lacZ*
	ED Fig. 6e-g	*w; mexGAL4, tubGAL80ts, 10XSTAT-GFP;* UAS-*his2A:RFP*
		w; mexGAL4, tubGAL80ts, 10XSTAT-GFP; UAS-*E-cad* RNAi
	ED Fig. 6h-j	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP, cycE-lacZ*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, *cycE-lacZ*
	ED Fig. 6k	*w; mexGAL4, tubGAL80ts;* UAS-*E-cad* RNAi, *Su(H)-lacZ*
	ED Fig. 6l	*w; upd3.1-lacZ*
ED Figure 7	ED Fig. 7a-b	*w; mexGAL4, tubGAL80ts;* UAS-*CD4:GFP* (qPCR reference)
	ED Fig. 7a	*w; mexGAL4, tubGAL80ts;* UAS-*E-cad* RNAi
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, UAS-*groucho*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, UAS-*puc2A*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, UAS-*yki* RNAi
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, UAS-*arm* RNAi
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, UAS-*p120* RNAi
	ED Fig. 7b	UAS-*arm*^{S10}*; mexGAL4, tubGAL80ts*
		w; mexGAL4, tubGAL80ts; UAS-*p120*
	ED Fig. 7c-f	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP, rho*^{X81}*(rho-lacZ)*
		w; mexGAL4, tubGAL80ts; UAS-*E-cad* RNAi, *rho*^{X81}
		w; mexGAL4, tubGAL80ts; UAS-*E-cad, rho*^{X81}
		UAS-*arm*^{S10}*; mexGAL4, tubGAL80ts; rho*^{X81}
		w; mexGAL4, tubGAL80ts, UAS-*p120; rho*^{X81}

ED = Extended Data

Supplementary Table 1 (continued) | Experimental genotypes in each figure

Figure	Panels	Genotype
ED Figure 7	ED Fig. 7g-l	See genotypes in Extended Data Fig. 7a
(continued)		*w; mexGAL4, tubGAL80ts;* UAS-*E-cad* RNAi, UAS-*upd3* RNAi
		w; mexGAL4, tubGAL80ts, UAS-*arm* RNAi; UAS-*E-cad* RNAi, UAS-*p120* RNAi
	ED Fig. 7m-n, s	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP*
		w; mexGAL4, tubGAL80ts, UAS-*rho*
	ED Fig. 7o-r	Same as Extended Data Figure 7b
		w; mexGAL4, tubGAL80ts; UAS-*rho* RNAi
		UAS-*arm*^{S10}*; mexGAL4, tubGAL80ts;* UAS-*p120*
ED Figure 8	ED Fig. 8a-d	*w; mexGAL4, tubGAL80ts;* UAS-*his2A:RFP*
		w; mexGAL4, tubGAL80ts, UAS-*rho* RNAi
		w; mexGAL4, tubGAL80ts; UAS-*arm* RNAi
		w; mexGAL4, tubGAL80ts; UAS-*p120* RNAi

ED = Extended Data

Supplementary Table 2 | List of qPCR primers used in this study

Target	Forward Primer	Reverse Primer
vein	GAACGCAGAGGTCACGAAGA	GAGCGCACTATTAGCTCGGA
spitz	CGCCCAAGAATGAAAGAGAG	AGGTATGCTGCTGGTGGAAC
keren	CGTGTTTGGCAACAACAAGT	TGTGGCAATGCAGTTTAAGG
egfr	TGCATCGGCACTAAATCTCGG	GGAAGCTGAGGTCCAAATTCTC
argos	TGCTGTTGGGTGAATTTCAGG	CGACTGGTCCAGATGATCCA
star	AGCCCAGTCCTTCAAACCC	CCACAGTCTTTGGTTGGTTGC
rhomboid	GAGCACATCTACATGCAACGC	GGAGATCACTAGGATGAACCAGG
frizzled-3	TCTTGTGCCCGCAAAACTTTA	CCTAGAATGAGGGTCTCAGACG
senseless	GATCGTGACTTTGCCTTGACG	CCTGATAGTCCTGCTTGCTGT
expanded	GATGCTGGACACCGAACTCT	CTTGCTCTCGGGATCTGC
diap1	GAAAAAGAGAAAAGCCGTCAAGT	TGTTTGCCTGACTCTTAATTTCTTC
pointed	CTACGAGAAGCTGAGTCGCG	TATCGTTTGCCTGCCGTCTT
cyclin-E	ACAAATTTGGCCTGGGACTA	GGCCATAAGCACTTCGTCA
unpaired-1	CCTACTCGTCCTGCTCCTTG	TGCGATAGTCGATCCAGTTG
unpaired-2	GAGGGCAGCTACGACAGTG	GGAGAAGAGTCGCAGGTTGT
unpaired-3	AAATTCGACAAAGTCGCCTG	TTCCACTGGATTCCTGGTTC
windpipe	TGGCAACCACAATGAGGAACAG	GACCGAGAAGACCTTCCAGTCAAC
Socs36E	CAGTCAGCAATATGTTGTCG	ACTTGCAGCATCGTCGCTTC
mef2	ATCGGCAGGTGACCTTCAAC	GTTGTACTCGGTGTACTTGAGCAG

All primers listed 5' to 3'. Sequences from [16], [28], and FlyPrimerBank (http://www.flyrnai.org/).