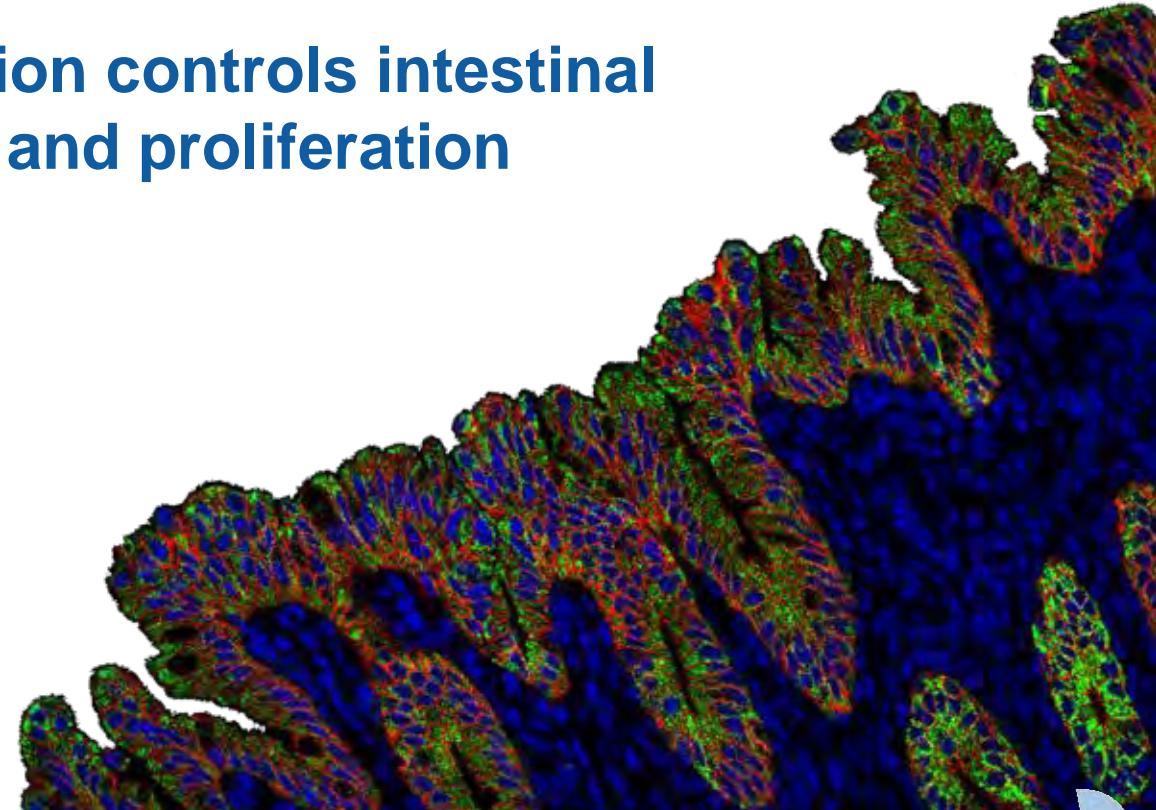


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Mitochondrial function controls intestinal epithelial stemness and proliferation



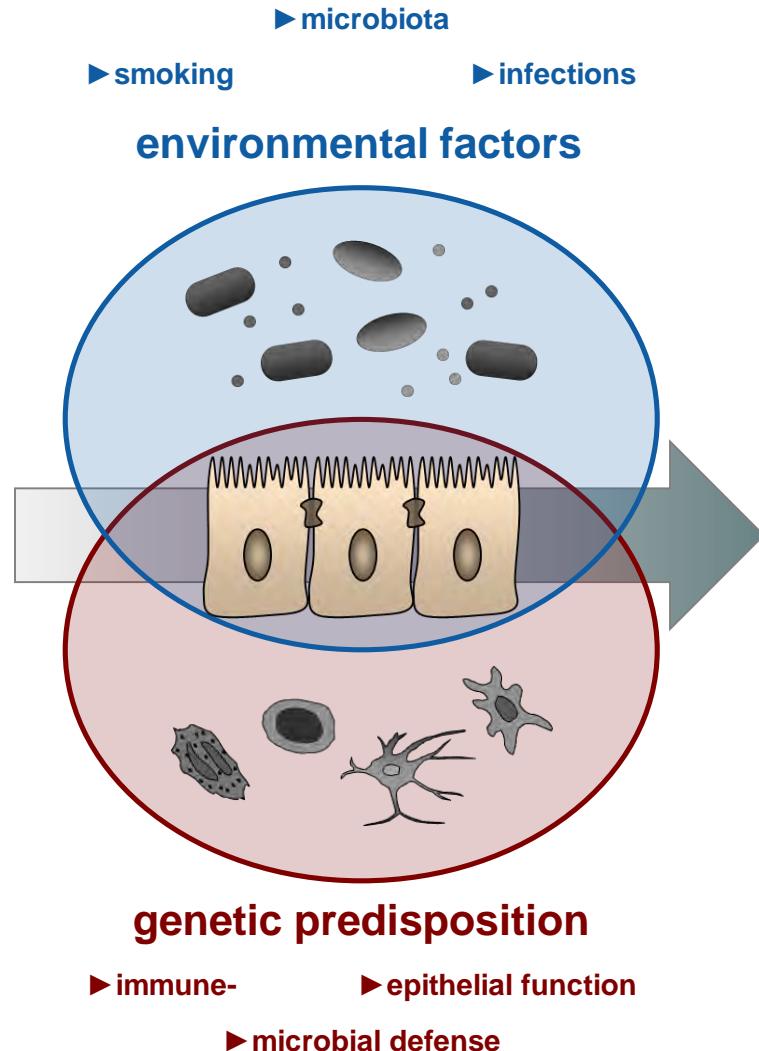
NuGO Week 2016



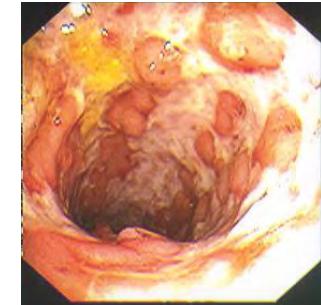
Inflammatory bowel diseases (IBD)



Healthy



Crohn's disease (CD)



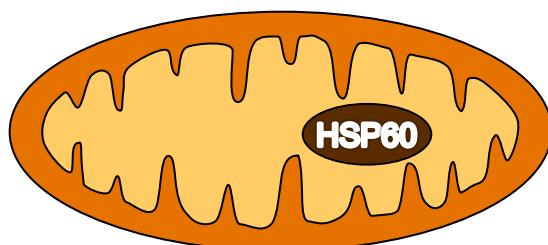
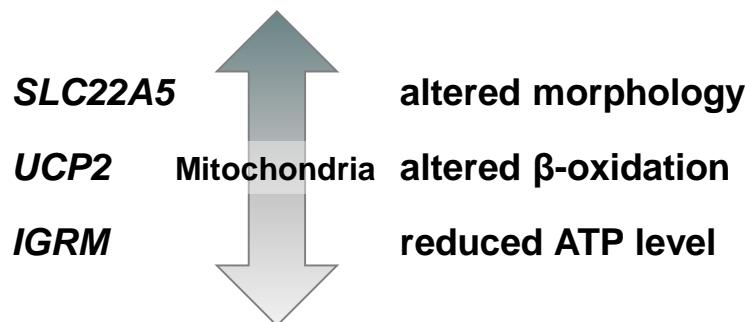
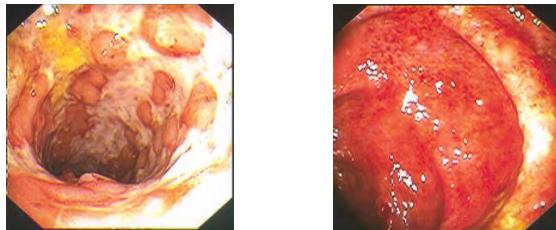
epithelial and immune dysfunction



Ulcerative colitis (UC)

Mitochondria in IBD – metabolic alterations & mt unfolded protein response

Crohn's disease Ulcerative colitis



The colonic epithelium in ulcerative colitis: an energy-deficiency disease?
Roediger, WE 1980, *Lancet*

Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate.

Lewis et al. 2010, *Inflamm Bowel Dis*

A mitochondrial specific stress response in mammalian cells

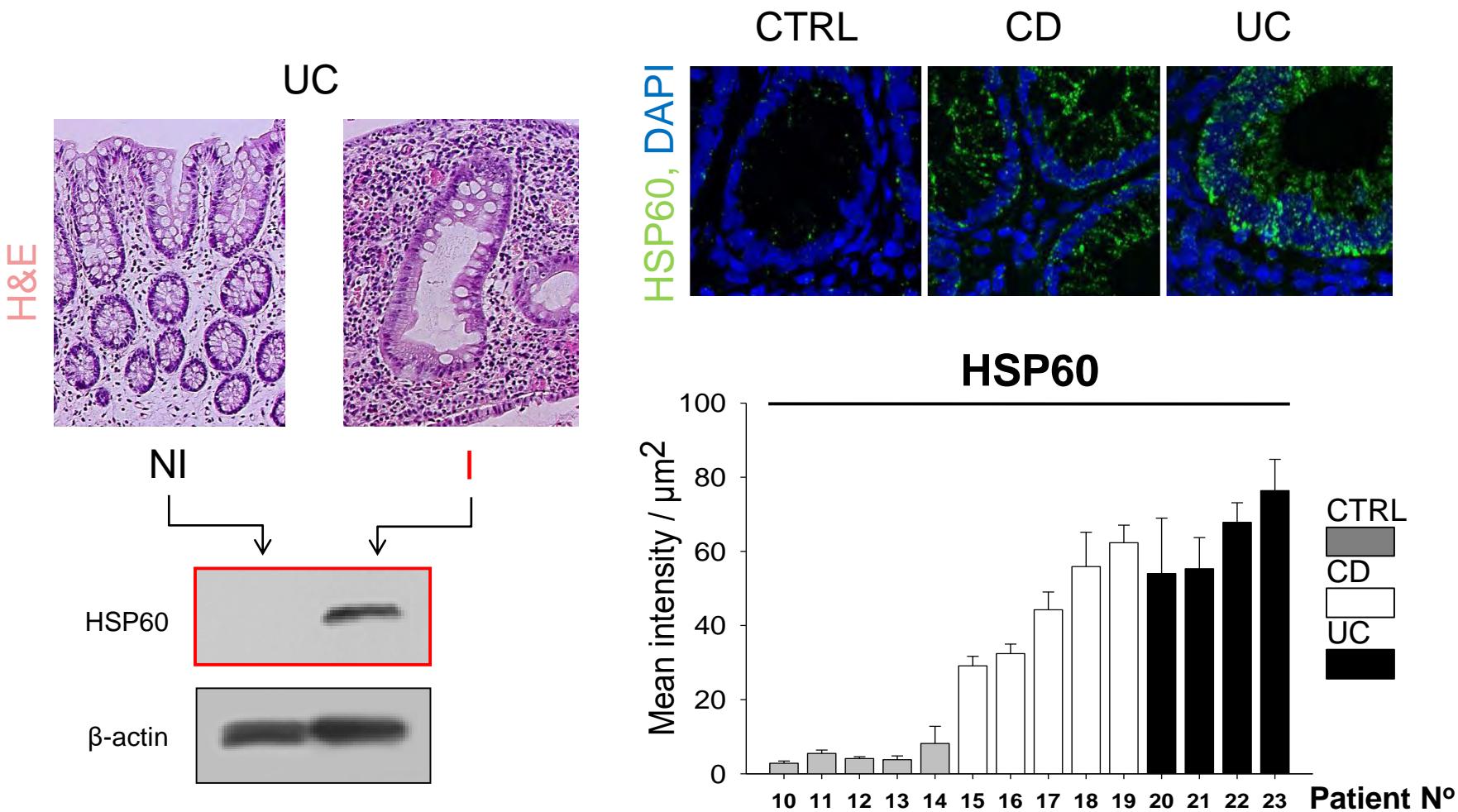
Zhao et al. 2002, *EMBO J.*

Induction of dsRNA-activated protein kinase links mitochondrial unfolded protein response to the pathogenesis of intestinal inflammation.

Rath et al. 2012, *Gut*



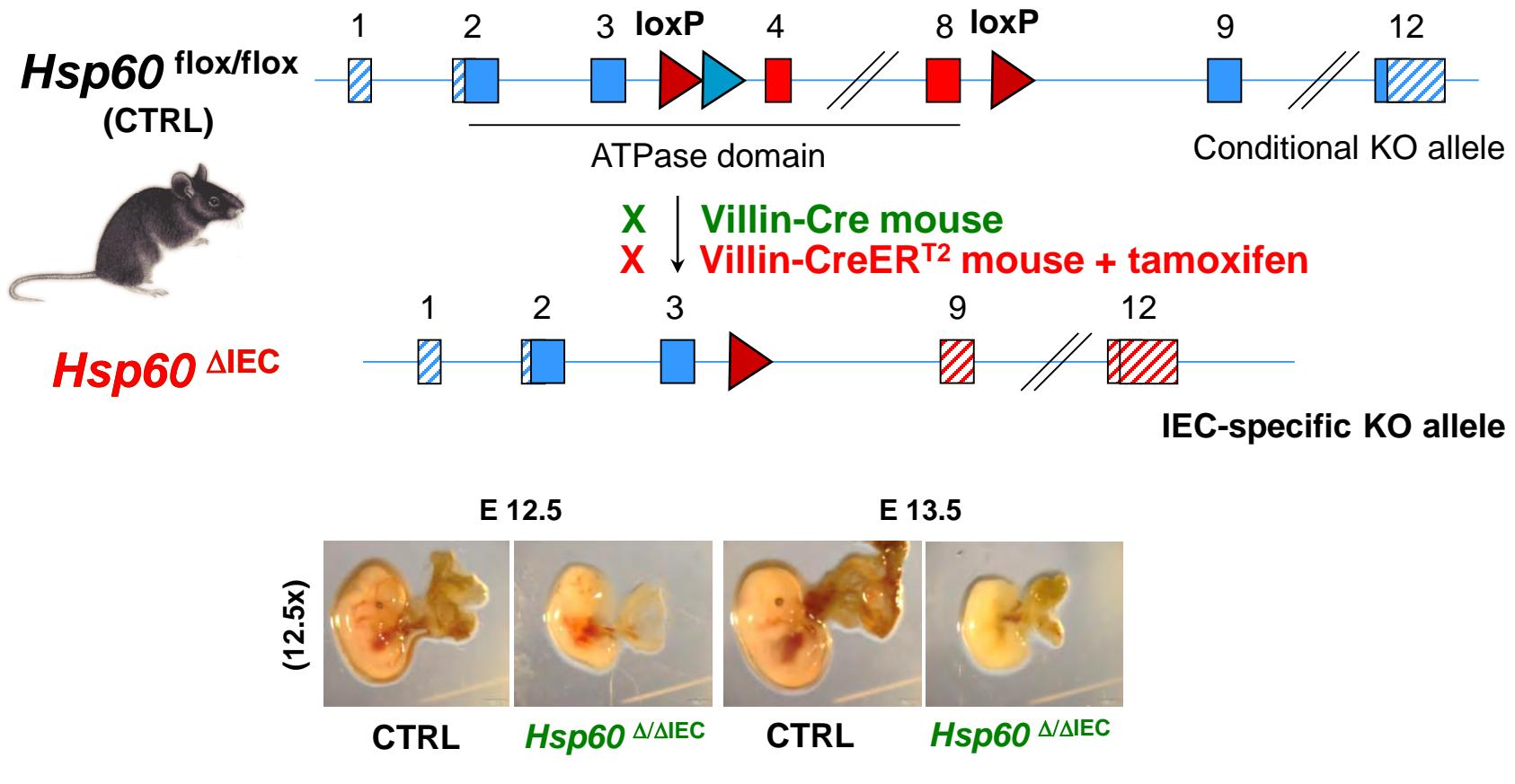
The mitochondrial chaperone HSP60 - increased expression in the epithelium of UC and CD patients



Functional role of HSP60 in the intestinal epithelium?



A new mouse model – tissue specific deletion of *Hsp60*



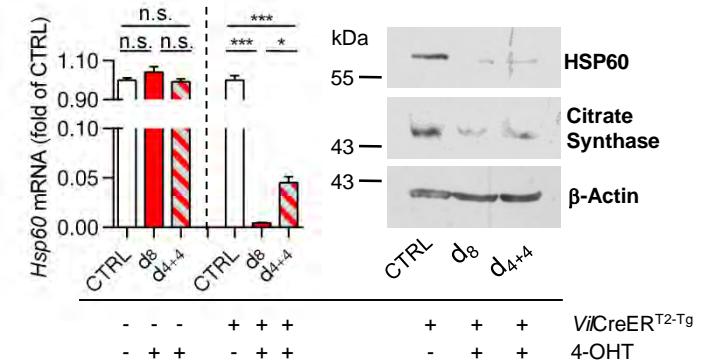
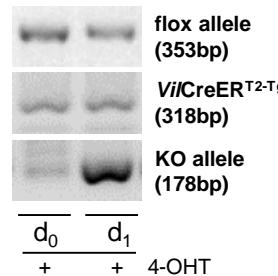
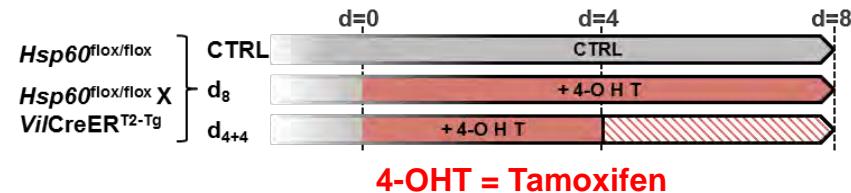
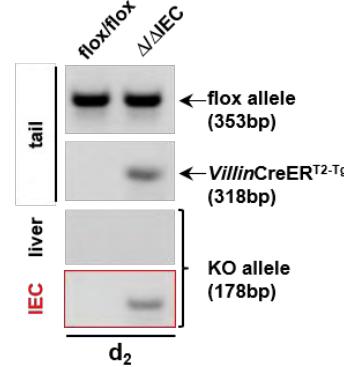
■ ■ mouse *Hspd1* exons □ mouse UTRs ▨ frameshift ▲ F3 ▶ loxP



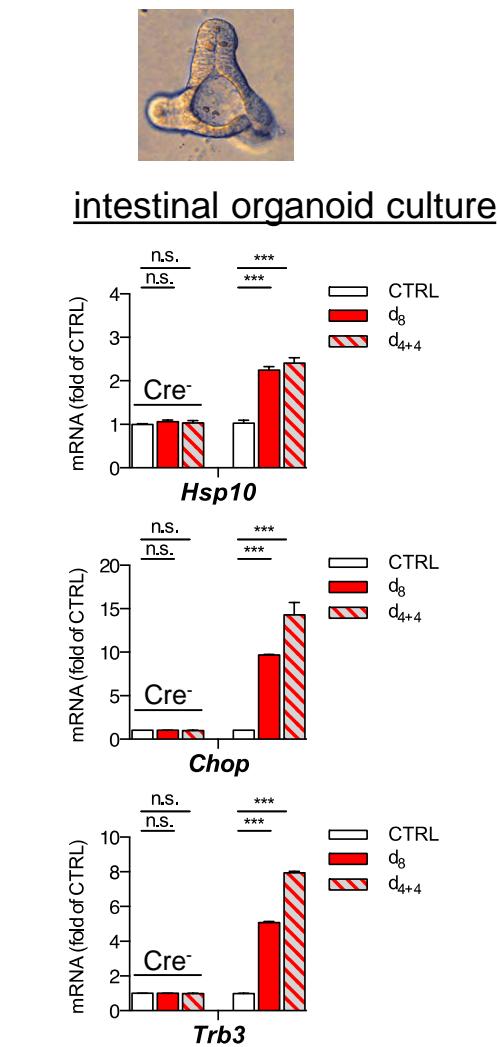
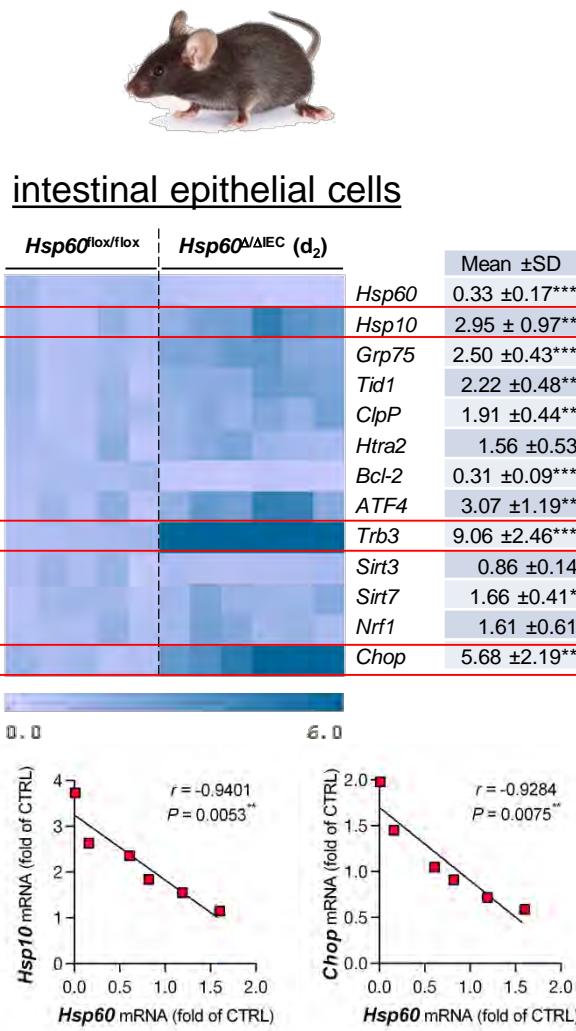
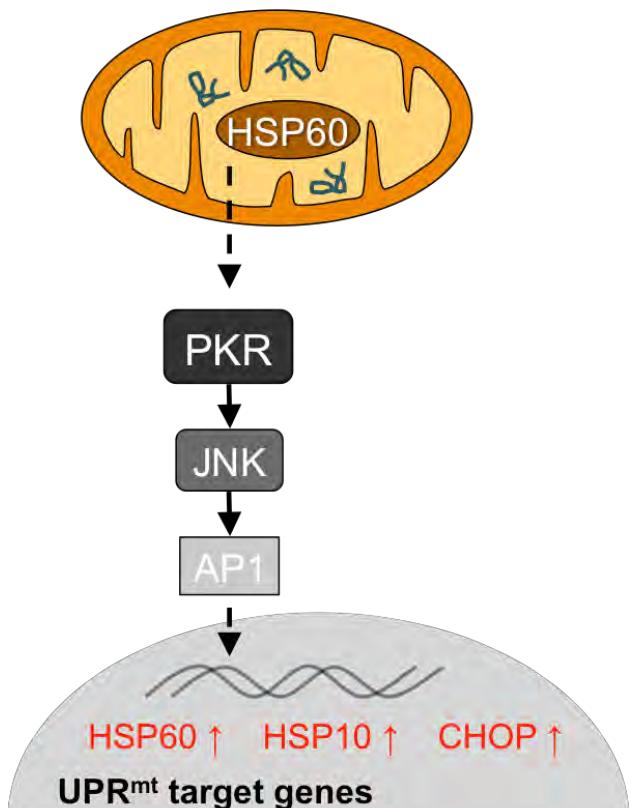
Hsp60 knockout in intestinal epithelial cells (IEC) – in vivo vs. “ex vivo” induction in intestinal organoids



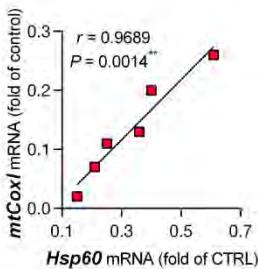
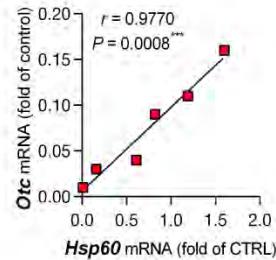
Hsp60^{flox/flox} X *VillinCreER*^{T2-Tg}
Tamoxifen
7 days → time
 d_2



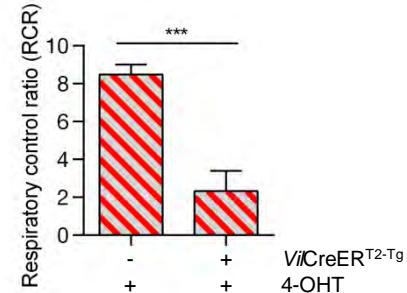
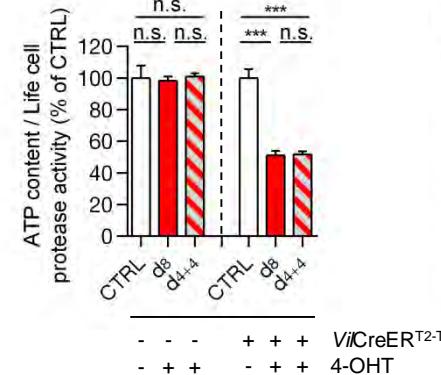
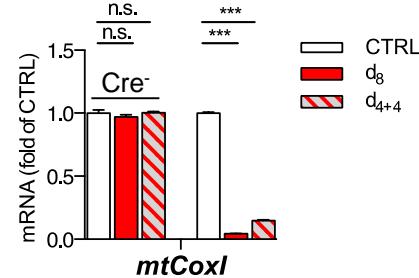
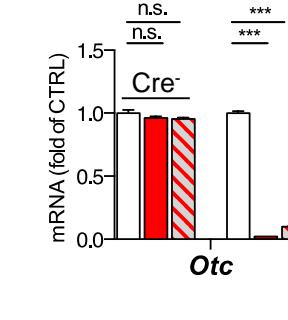
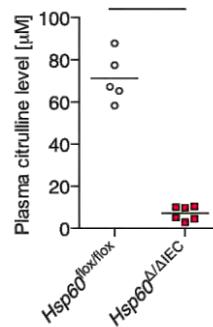
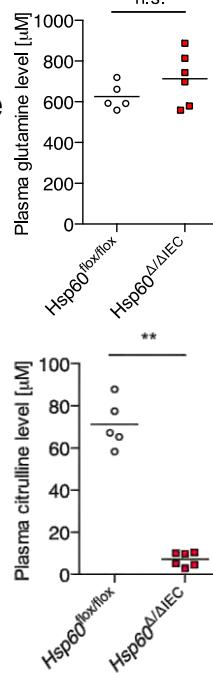
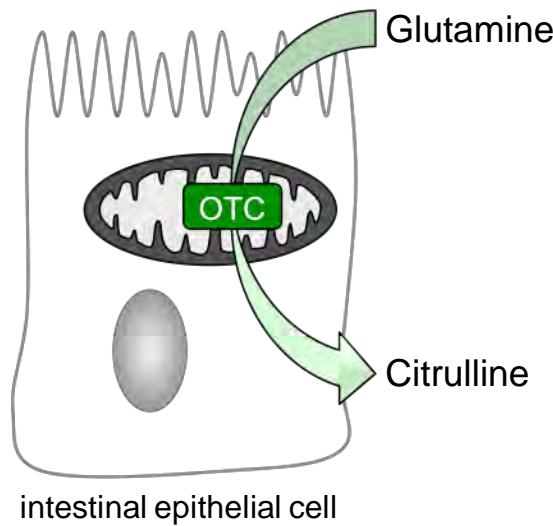
Hsp60 knockout in intestinal epithelial cells (IEC) – induction of mitochondrial unfolded protein response



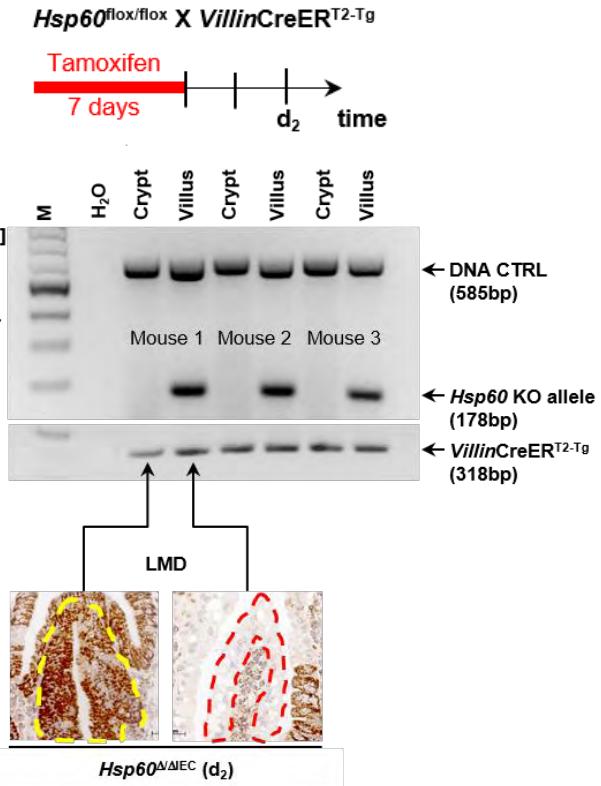
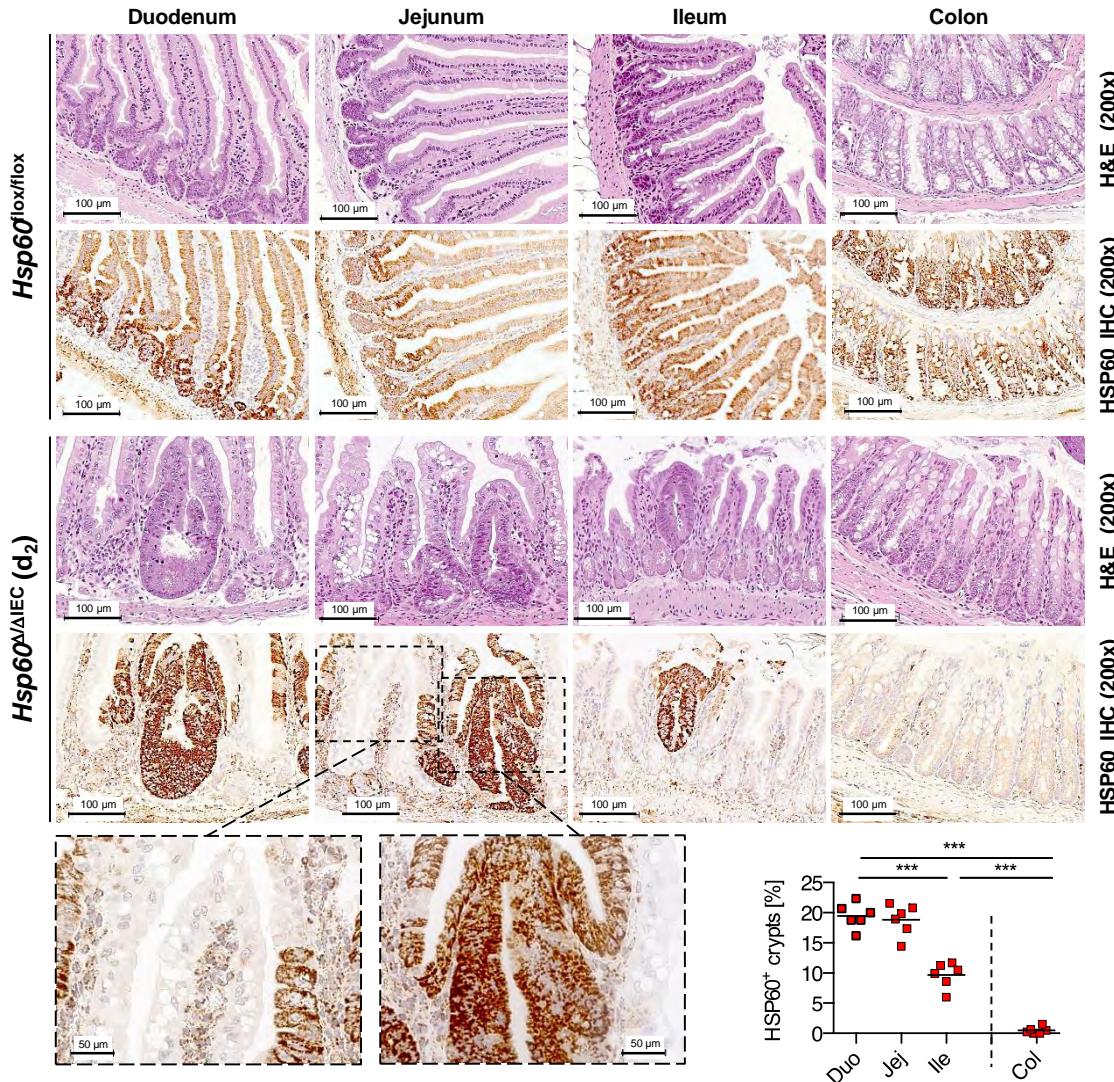
Hsp60 knockout in intestinal epithelial cells (IEC) – induction of mitochondrial dysfunction



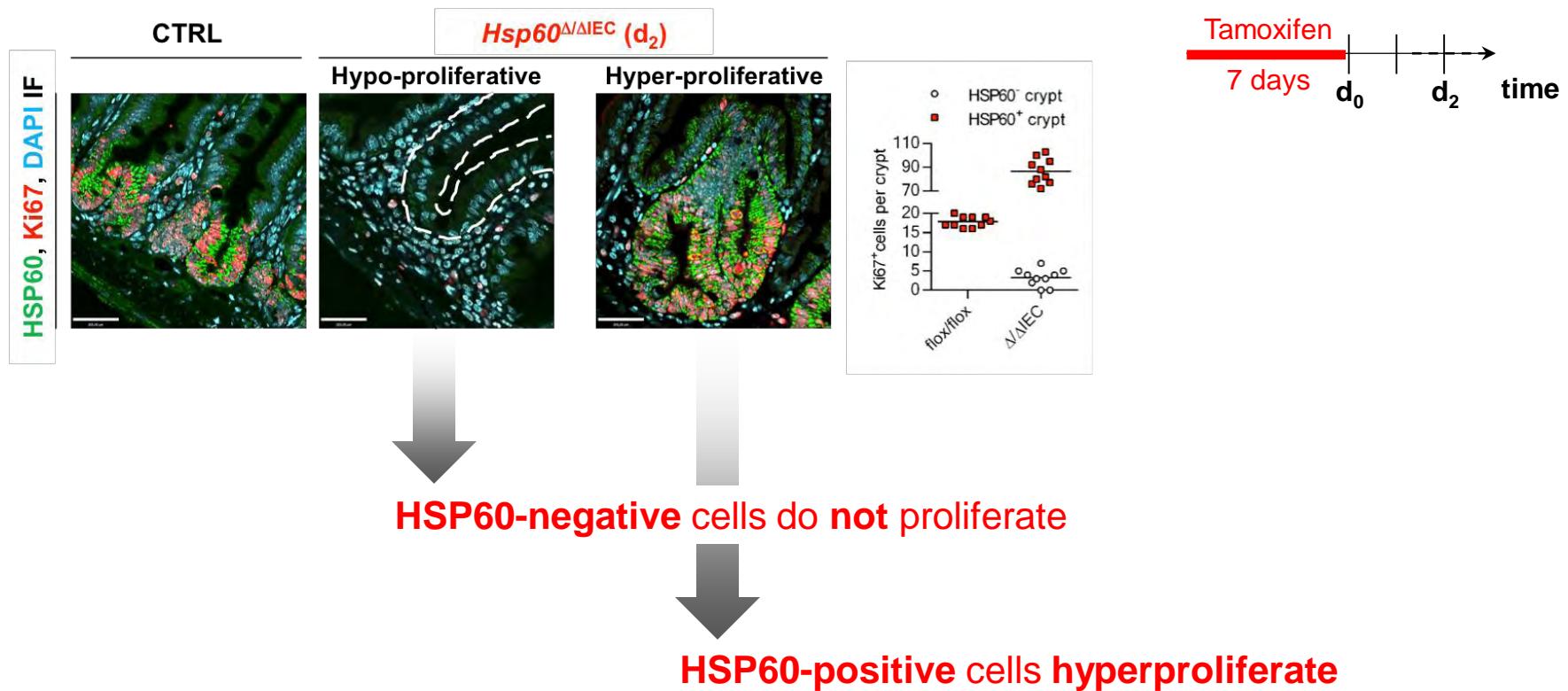
Ornithine transcarbamylase



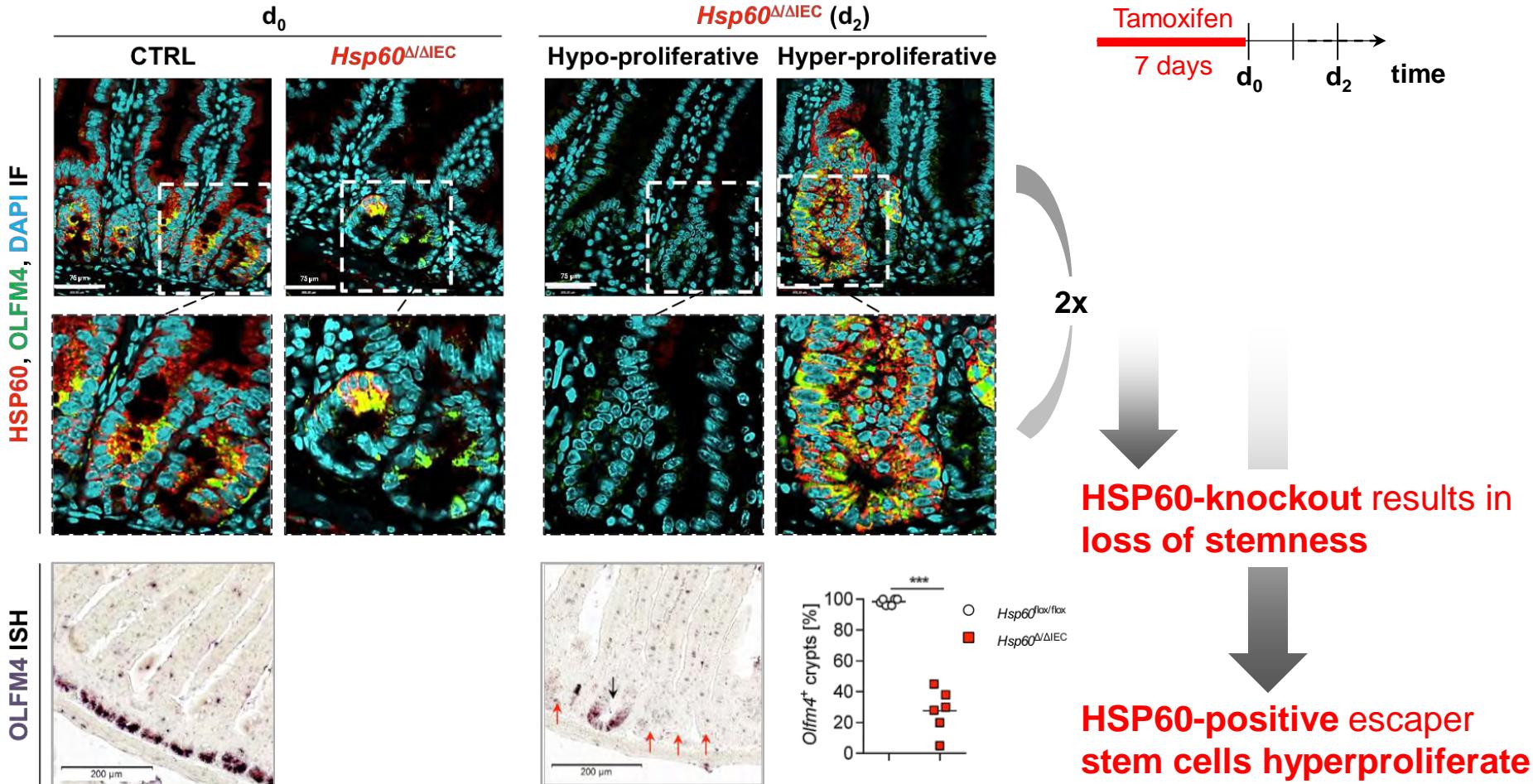
Hsp60 knockout in intestinal epithelial cells (IEC) – effect on tissue morphology



Hsp60 knockout in intestinal epithelial cells (IEC) – nodular structures are hyperproliferative

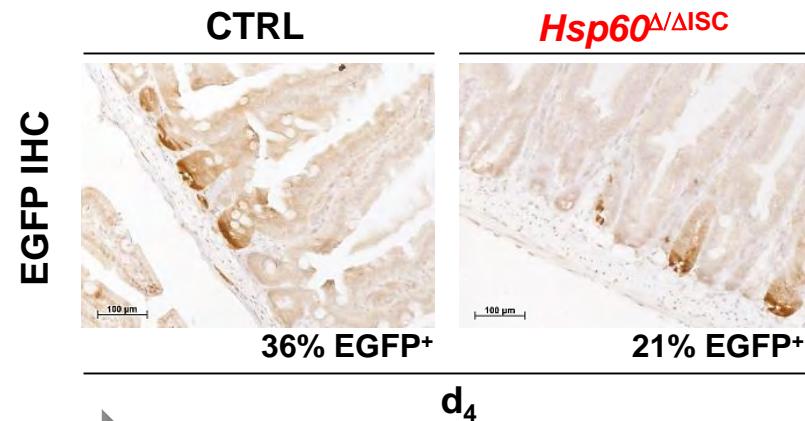
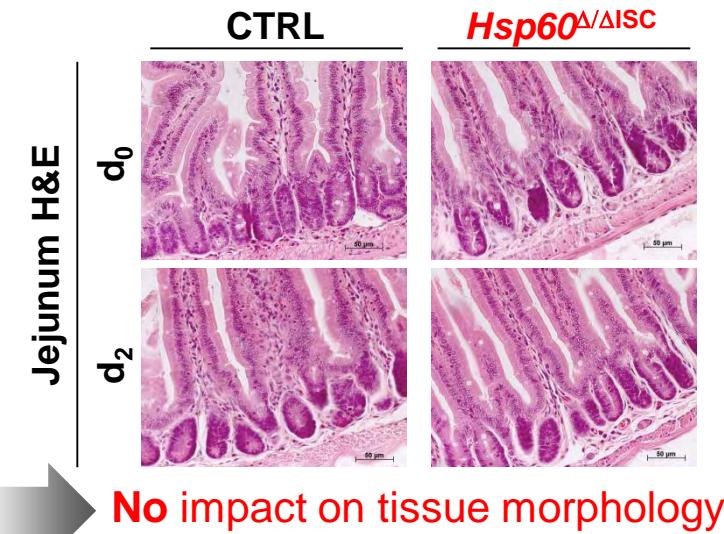
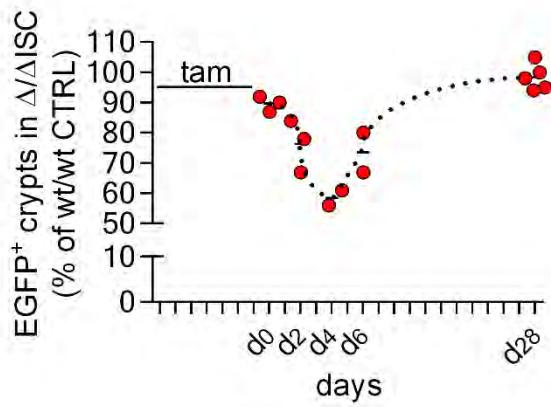
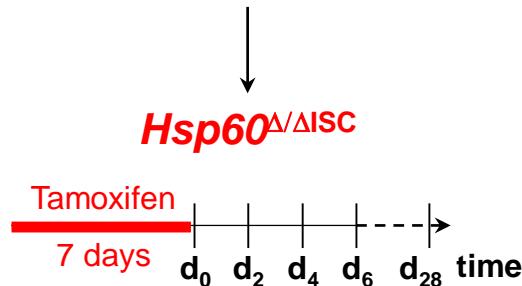


Hsp60 knockout in intestinal epithelial cells (IEC) – hyperproliferative nodules originate from *Olfm4*⁺ stem cells

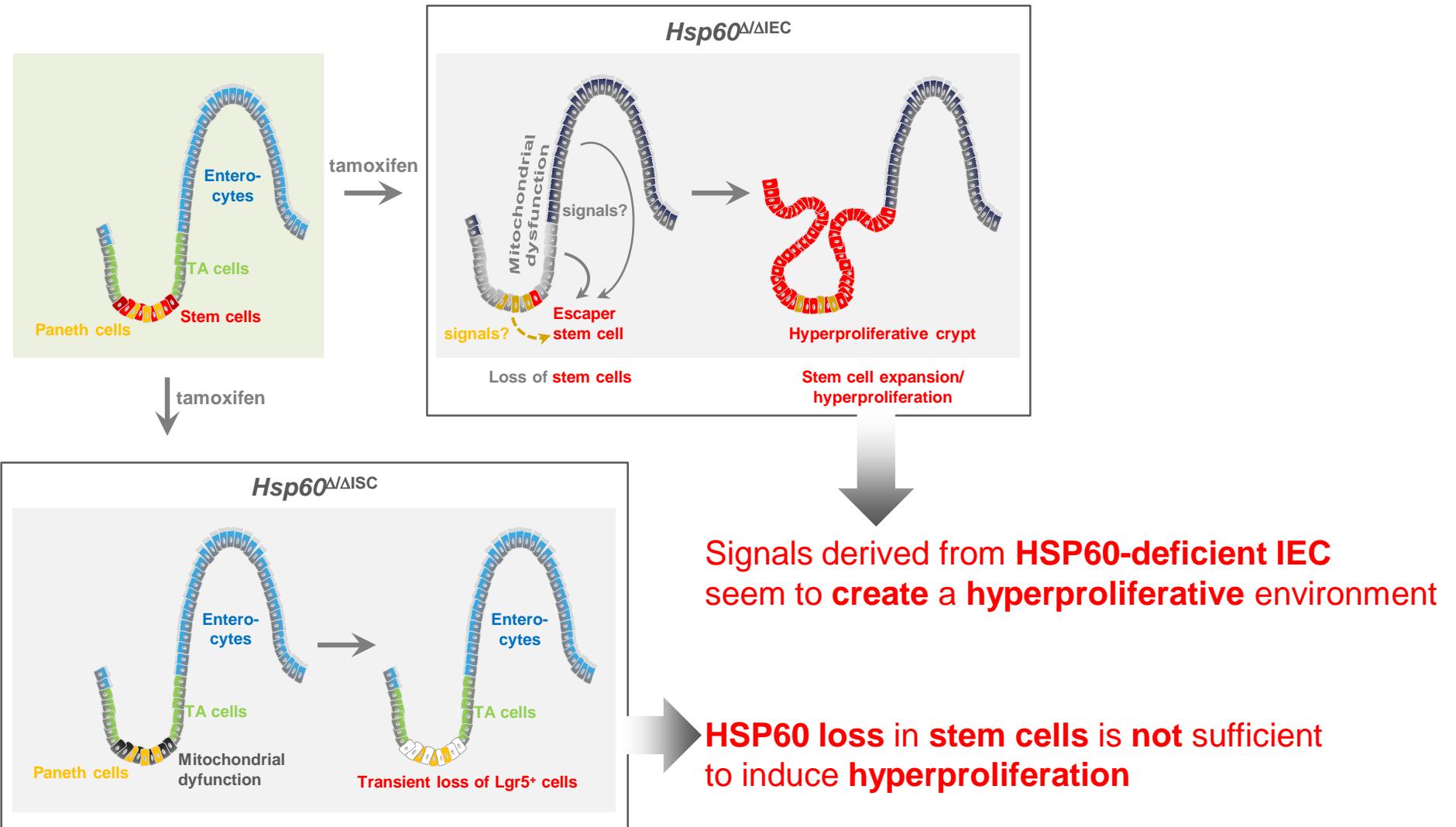


Hsp60 knockout in intestinal stem cells (ISC) – impact on Lgr5+ stem cells

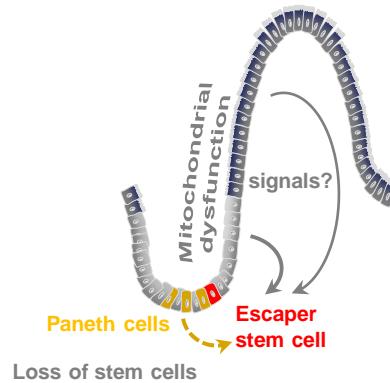
Hsp60^{flox/flox} X *Lgr5CreERT²-Egfp^{Tg}*
+ tamoxifen



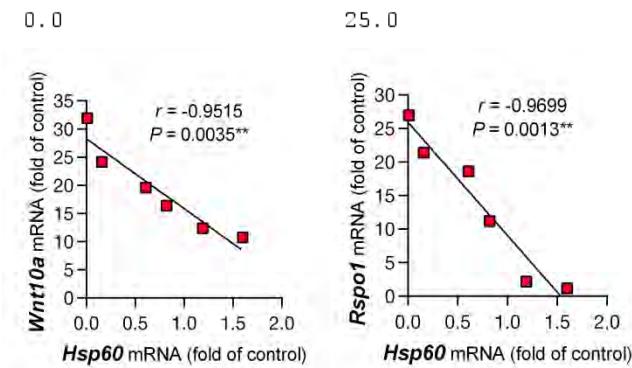
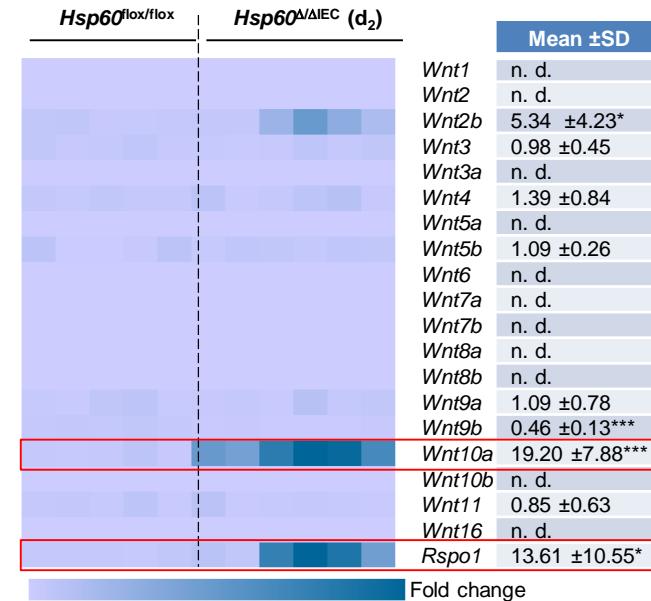
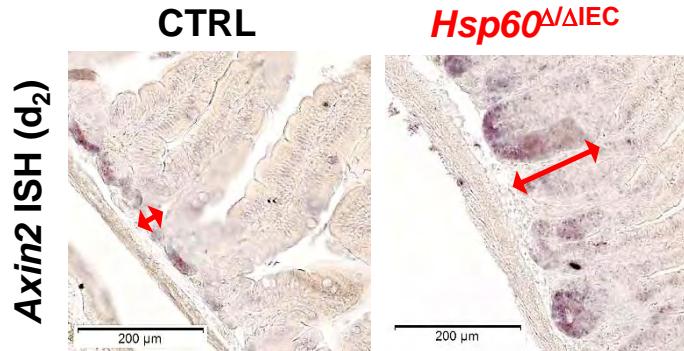
Hsp60 knockout in intestinal epithelial cells (IEC) – generation of a pro-proliferative environment



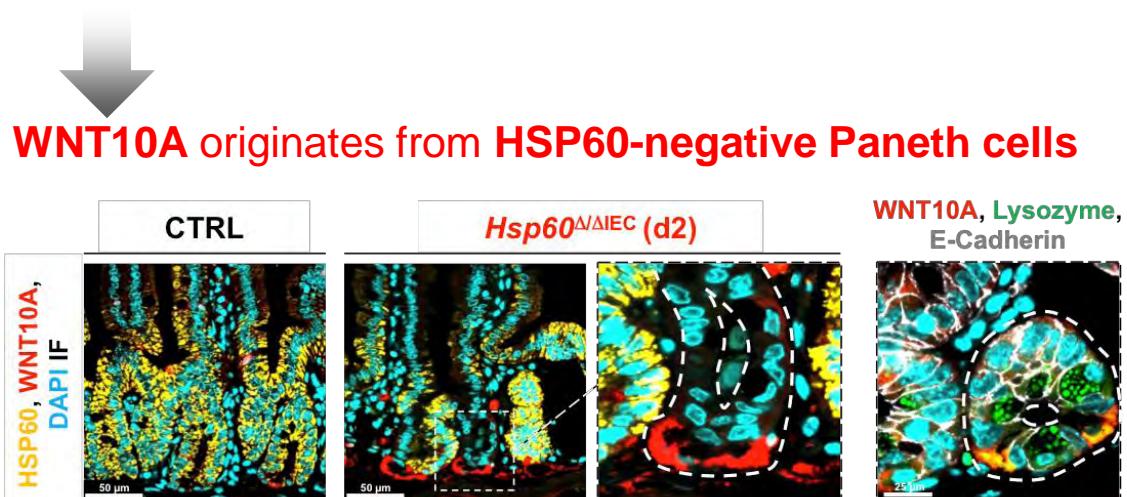
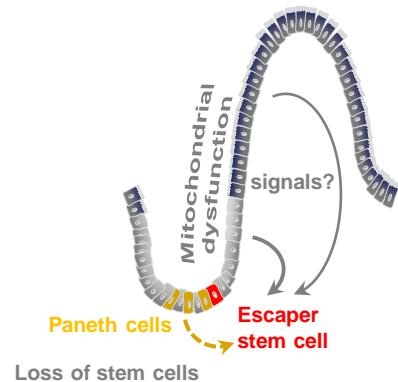
Hsp60 knockout in intestinal epithelial cells (IEC) – generation of a pro-proliferative environment



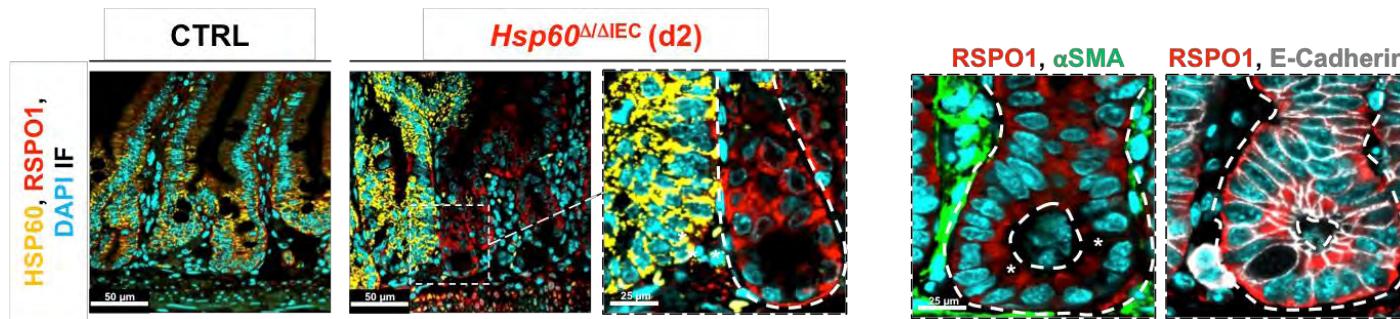
enhanced WNT-signaling



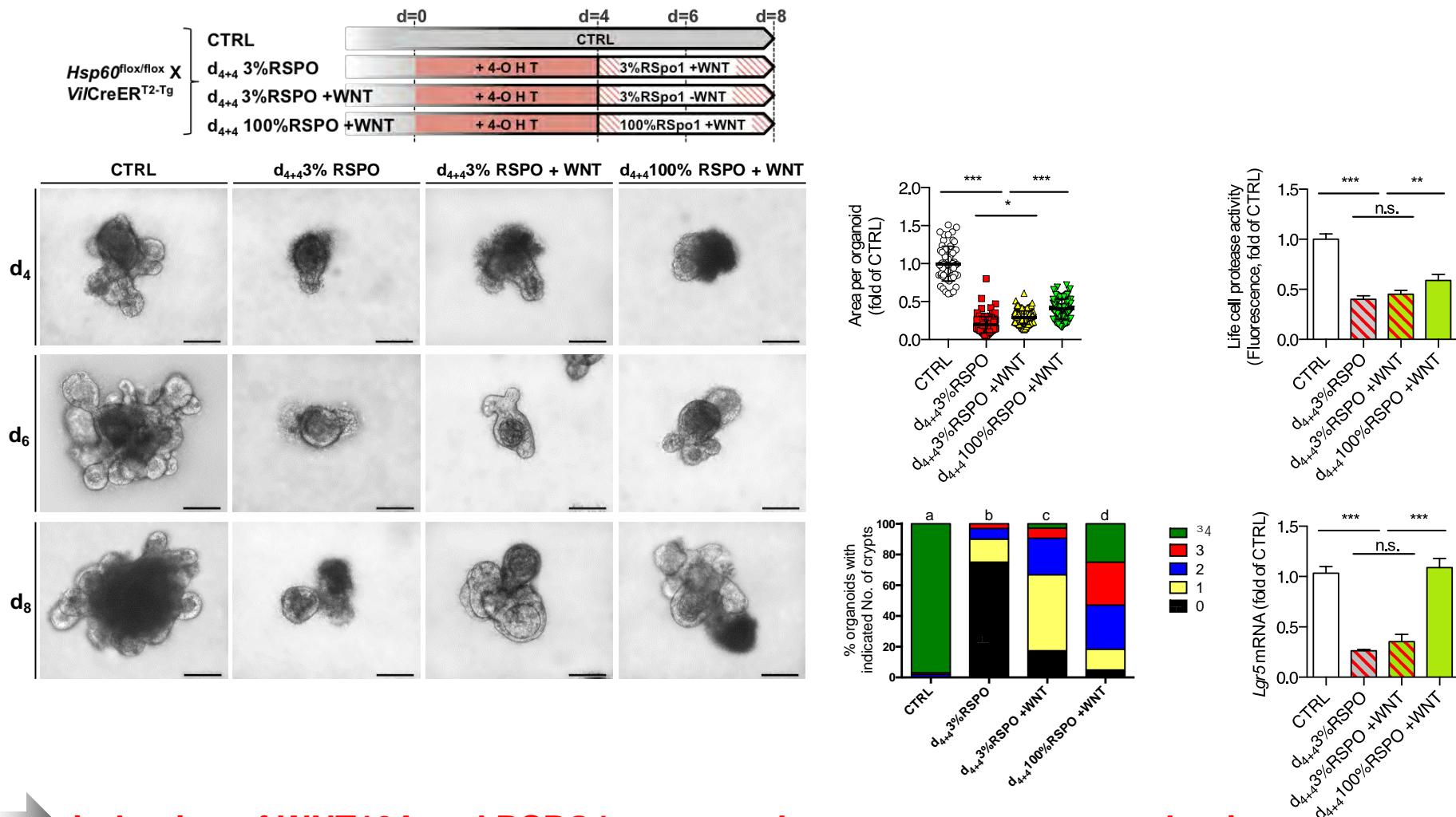
Hsp60 knockout in intestinal epithelial cells (IEC) – induction of WNT-related signals



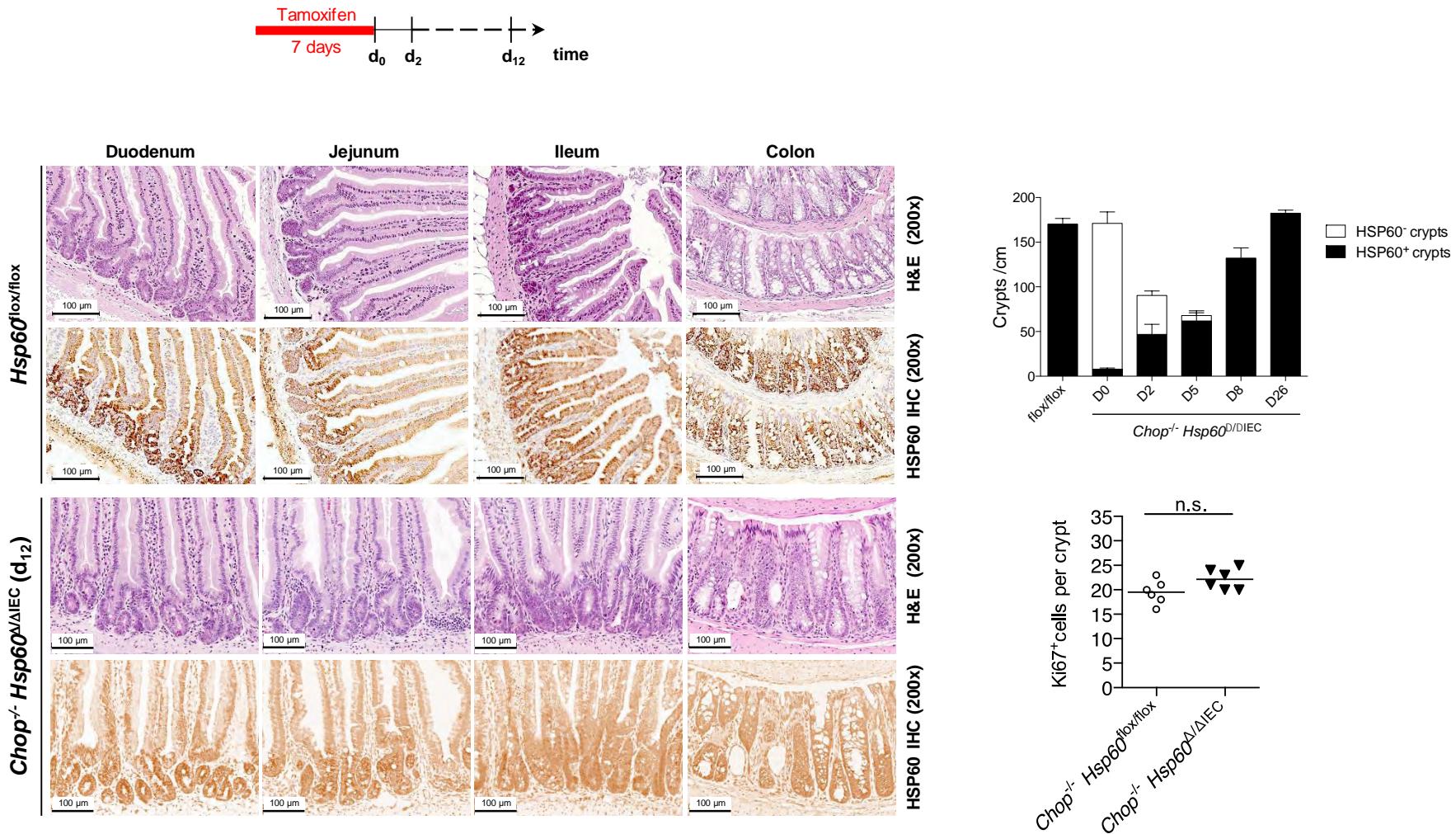
R-Spondin 1 originates from HSP60-negative IEC



Hsp60 knockout in intestinal epithelial cells (IEC) – role of RSPO1 and WNT10A in organoids



Hsp60 knockout in intestinal epithelial cells (IEC) – hyperproliferative nodules result in tissue reconstitution



Hsp60 knockout in intestinal epithelial cells (IEC) – summary

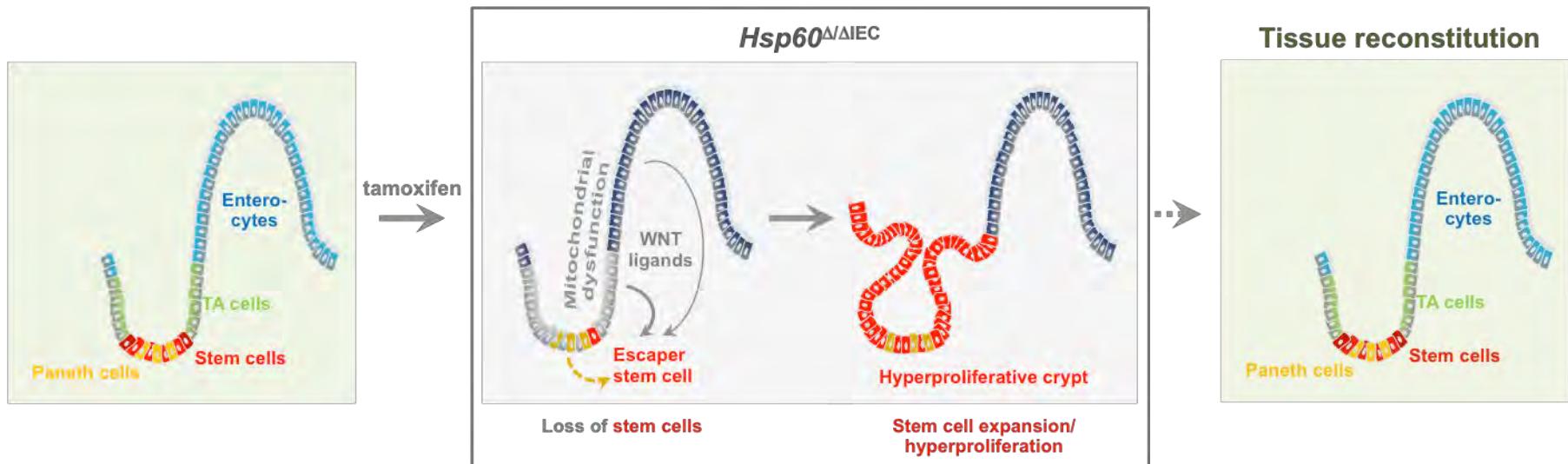
Loss of epithelial HSP60 triggers MT-UPR and mitochondrial dysfunction

Mitochondrial dysfunction antagonizes proliferation and stemness

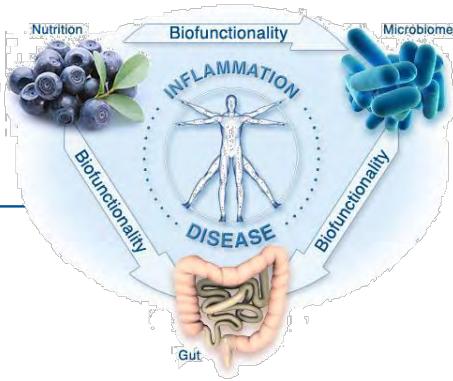
(ER Stress Causes Rapid Loss of Intestinal Epithelial Stemness through Activation of the Unfolded Protein Response. Heijmans et al., 2013, Cell Rep)

Mitochondrial dysfunction induces expression of WNT-related factors

Compensatory hyperproliferation results in tissue reconstitution



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