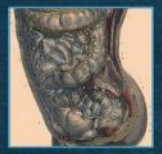
Life and death at the mucosal-luminal interface:

New perspectives on human intestinal ischemia-reperfusion



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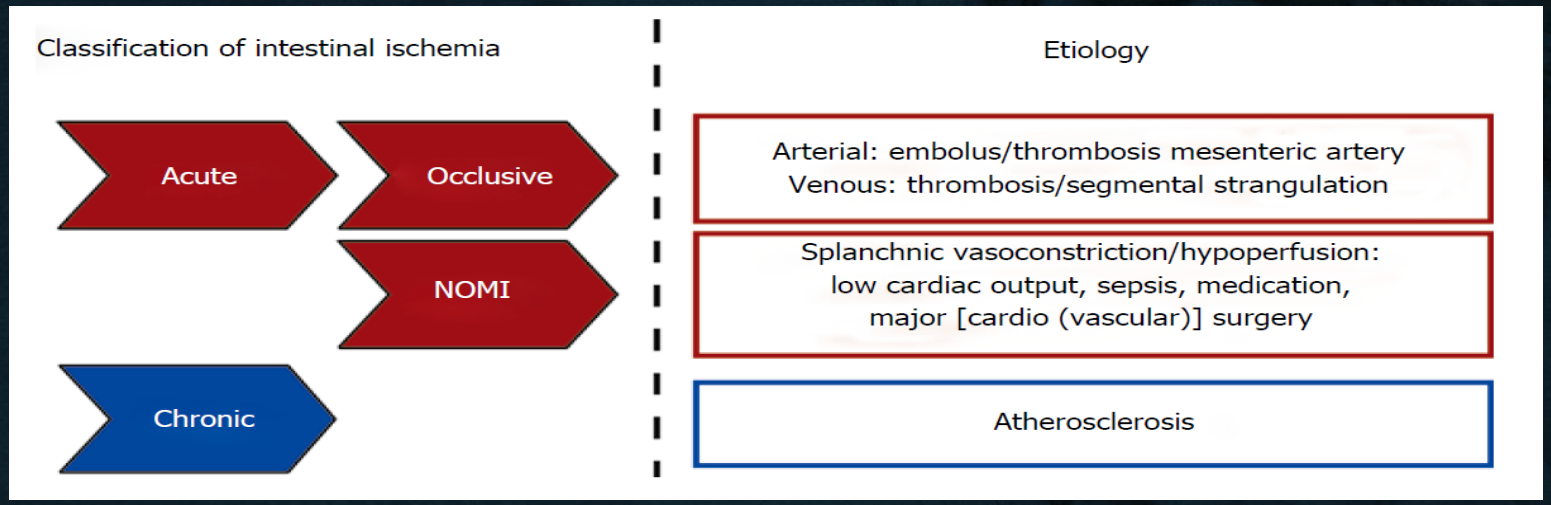
Disclosures

- None

Necrotizing enterocolitis (NEC)?

Intestinal ischemia-reperfusion (IR): a life-threatening phenomenon



Mortality remains >60%

AGA Guidelines. Gastroenterology. 2000

Grootjans, Derikx et al. WJG 2016

Factors associated with high mortality of intestinal IR

- Delayed diagnosis
  - Limited non-invasive diagnostic options
  - Early diagnosis reduces mortality by 50%

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- Delayed diagnosis
  - Limited non-invasive diagnostic options
  - Early diagnosis reduces mortality by 50%

- No preventive/therapeutic strategies
  - Limited knowledge on the pathophysiology of human intestinal IR

General aims of the project

New insights in human intestinal ischemia-reperfusion

- To facilitate early diagnosis of intestinal IR
- To elucidate the pathophysiology of human intestinal IR

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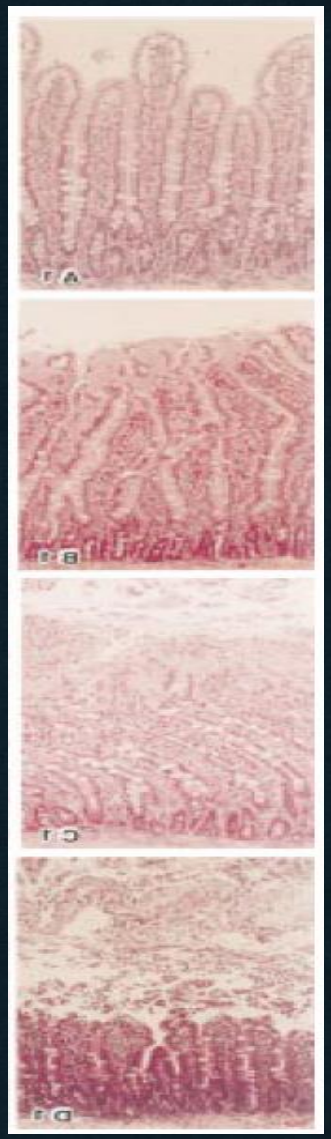
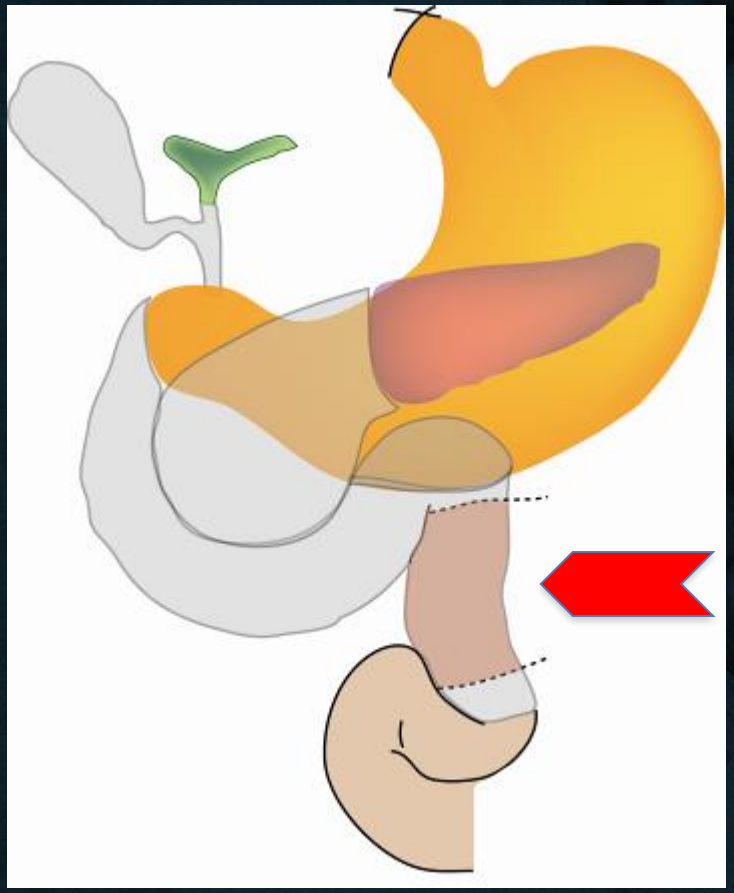
Pathophysiology: mainly animal studies

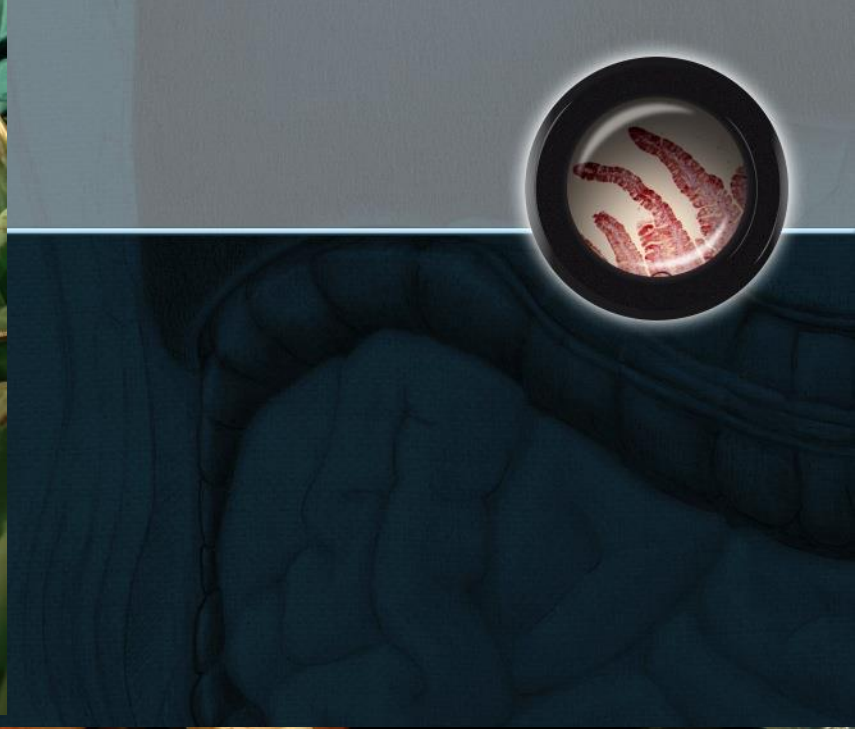


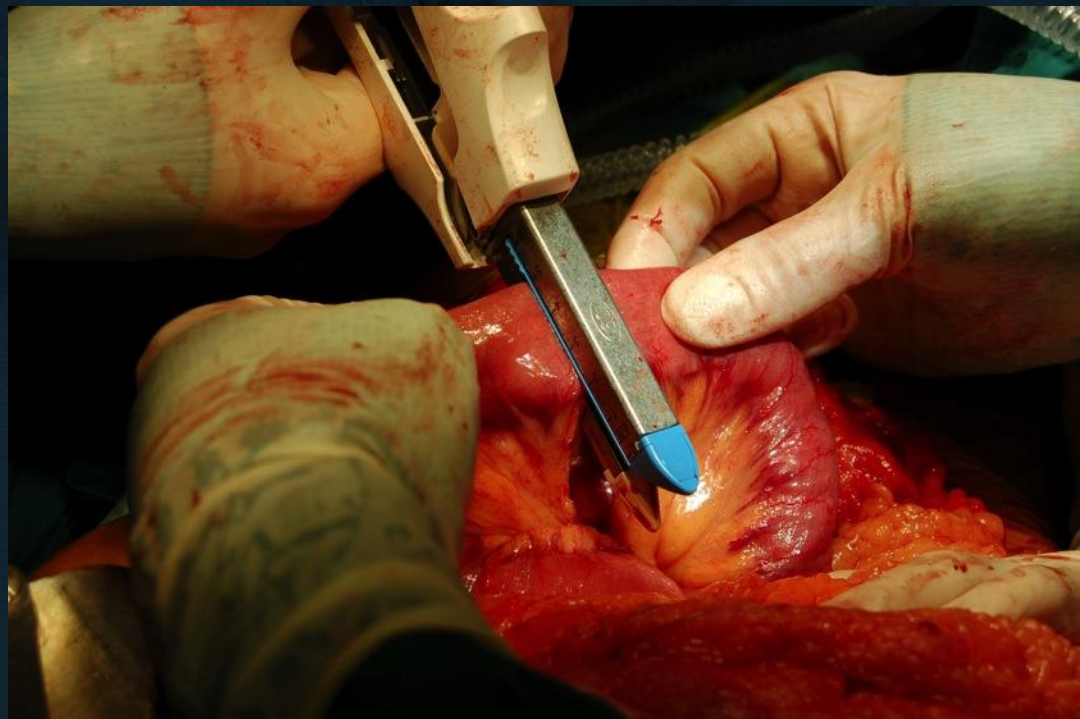
Park/Chiu
Chiu
0. Normal mucosa
1. Subepithelial space at villus tips
2. Extension of subepithelial space with moderate lifting
3. Massive lifting down sides of villi, some denuded tips
4. Denuded villi, dilated capillaries
5. Disintegration of lamina propria
Park
6. Crypt layer injury
7. Transmucosal infarction
8. Transmural infarction

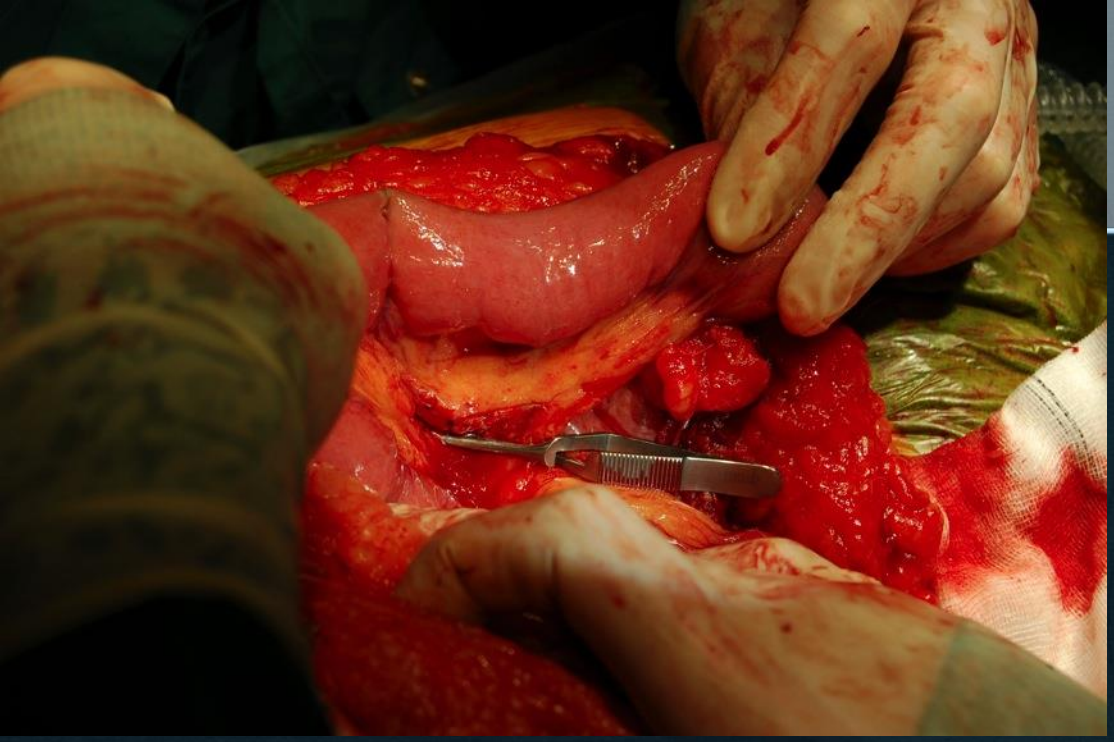
New model to study intestinal ischemia in man

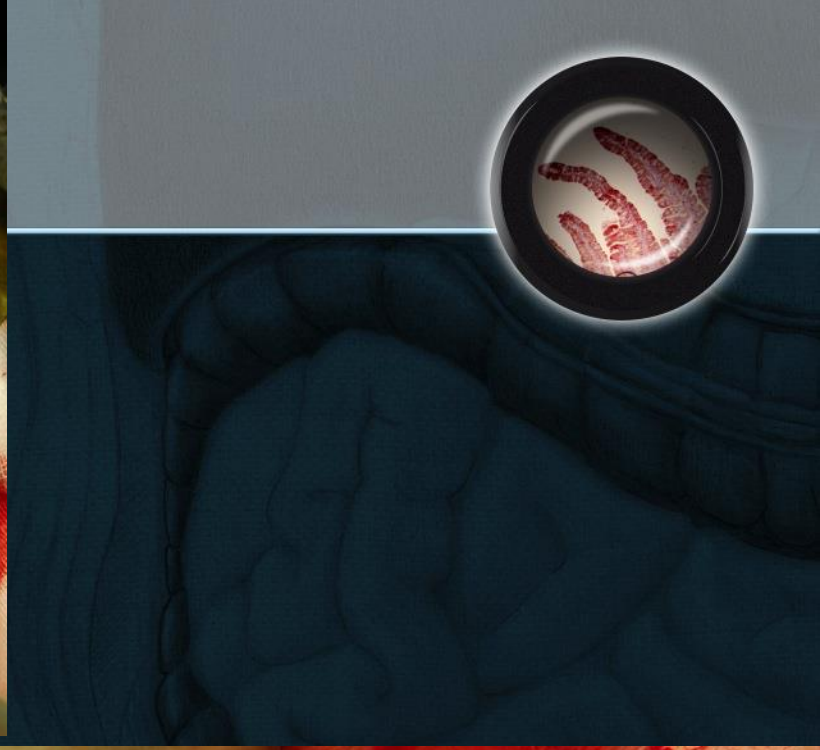


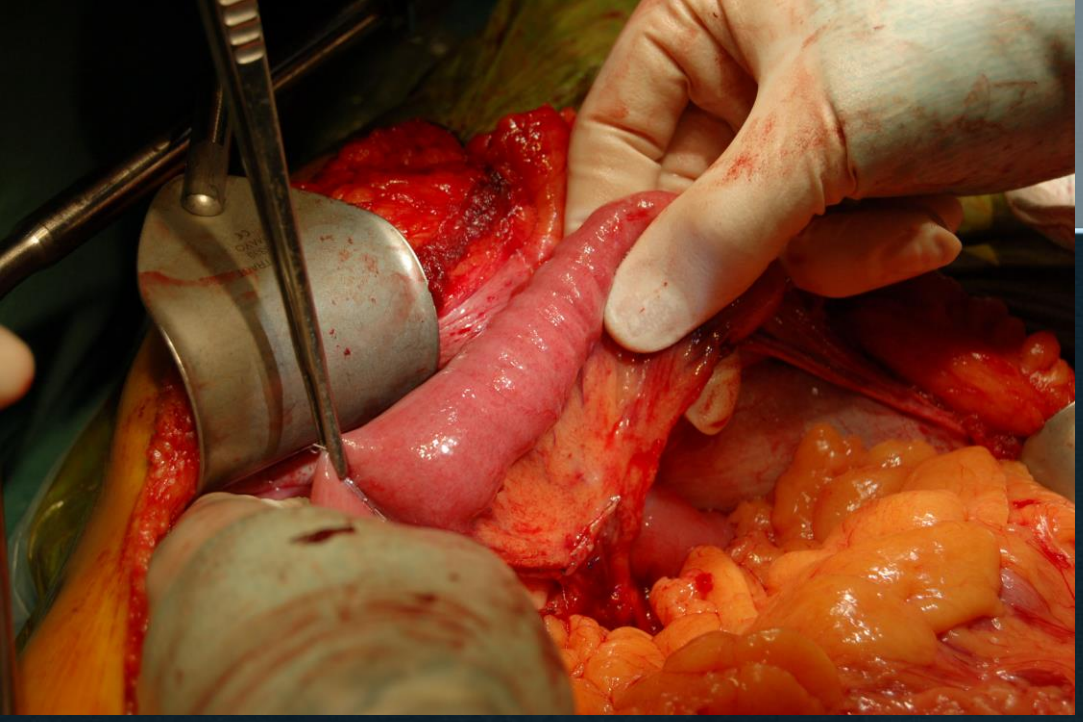
Derikx et al. Plos One 2008
Derikx et al. J Surg Res 2011

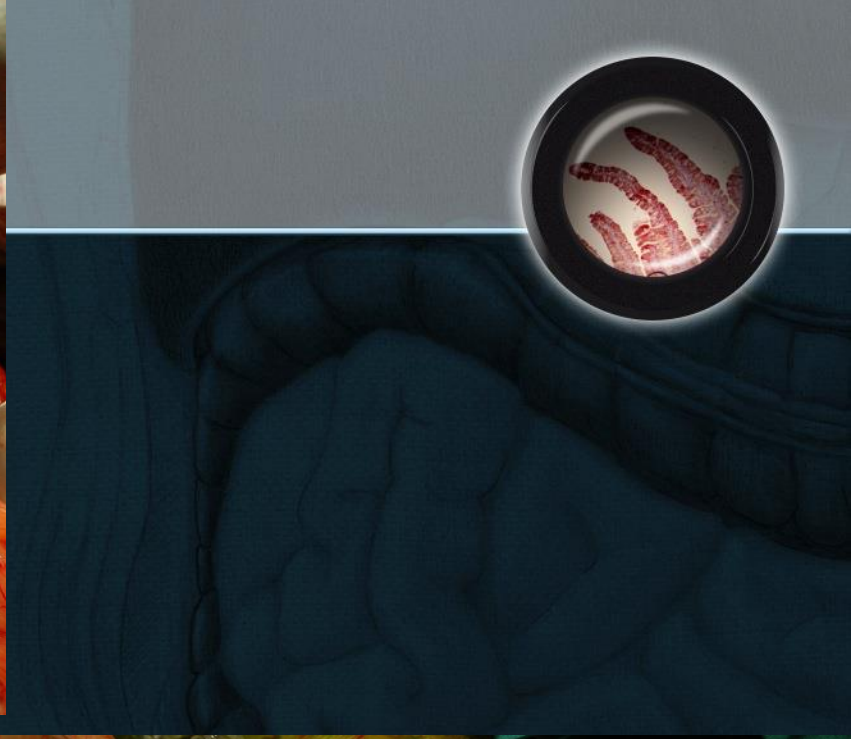


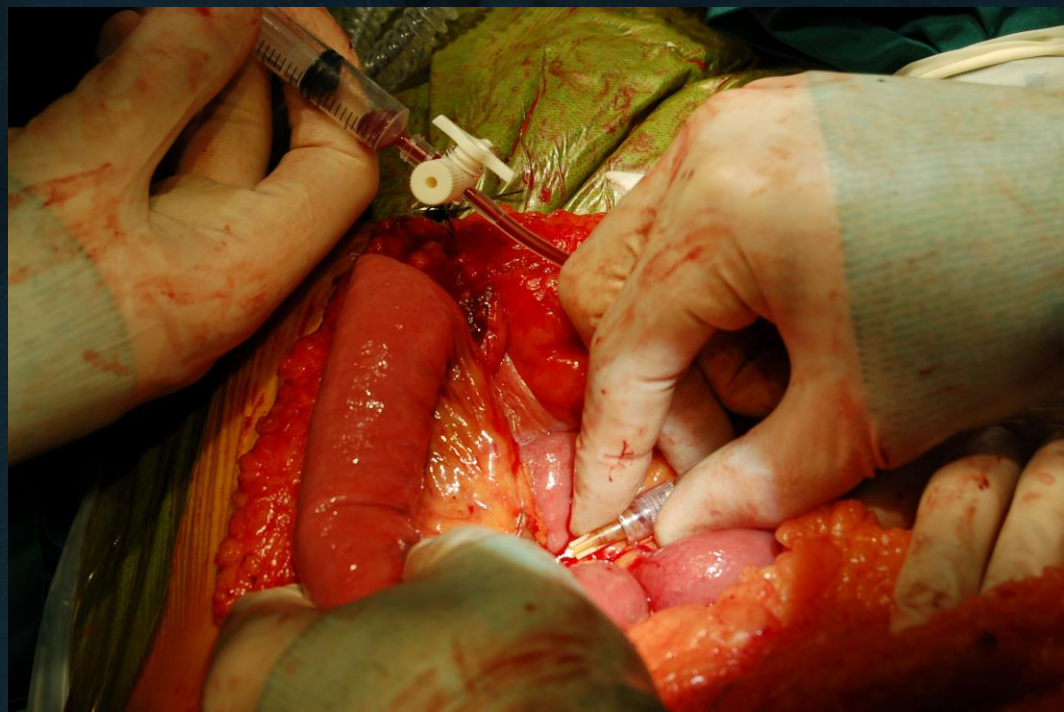






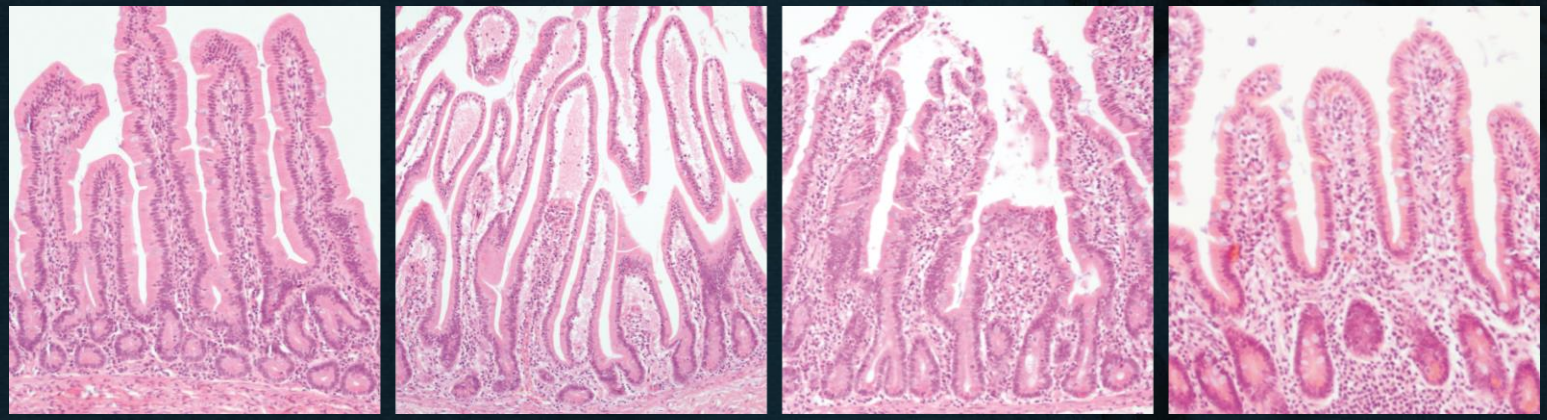






Short period of ischemia leads to reversible damage

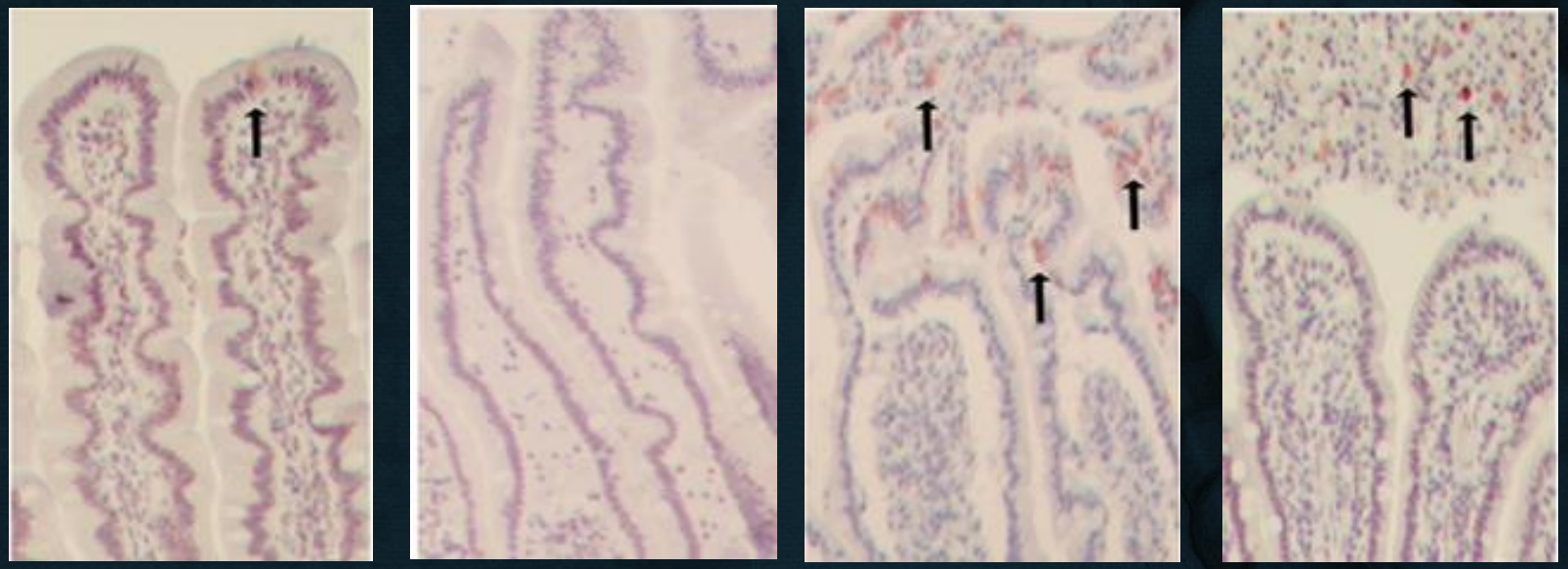
Control | 30I | 30I 30R | 30I 120R



Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011

Short period of ischemia leads to apoptosis of mature enterocytes

Control | 30I | 30I 30R | 30I 120R



Derikx et al. Plos One 2008
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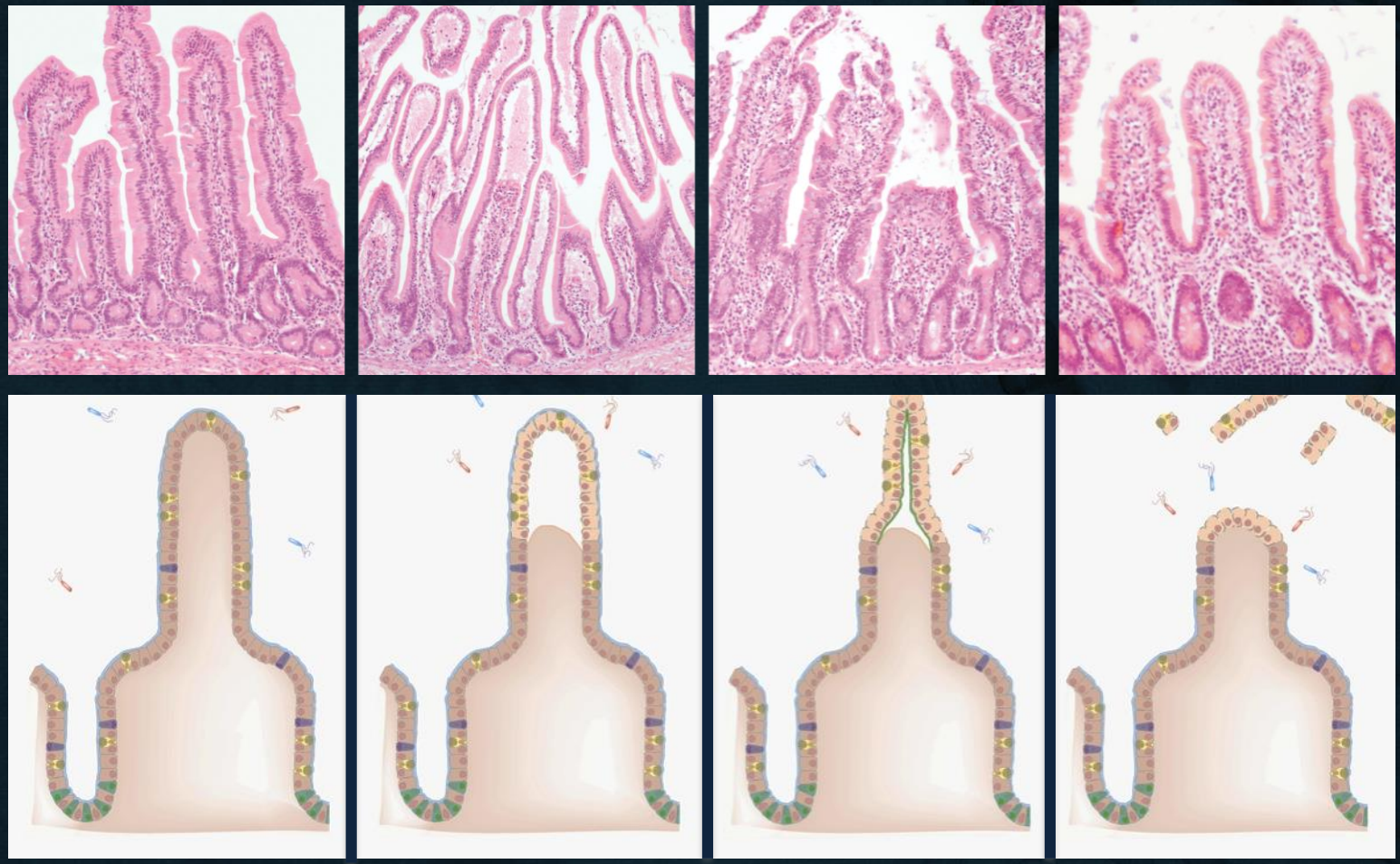
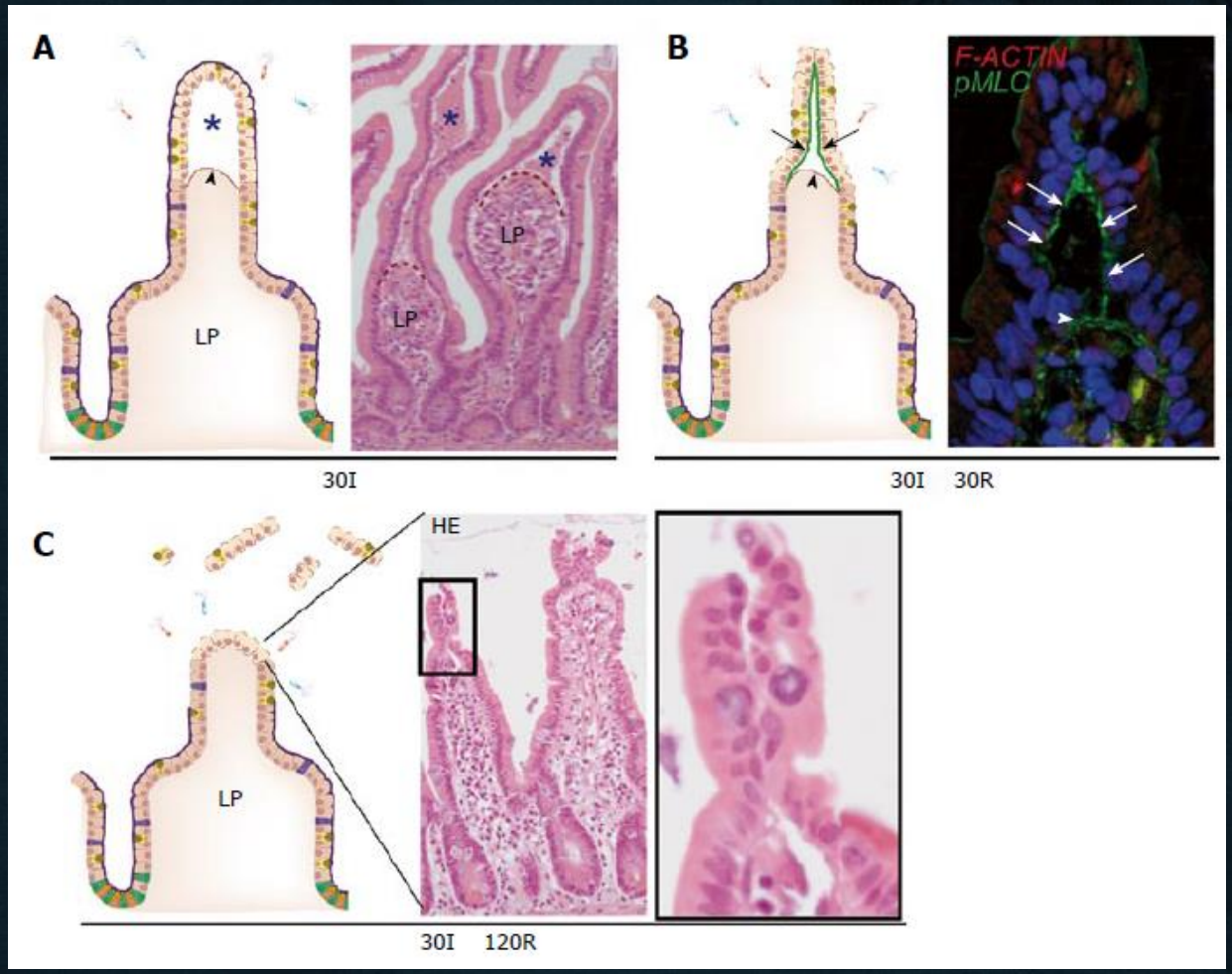


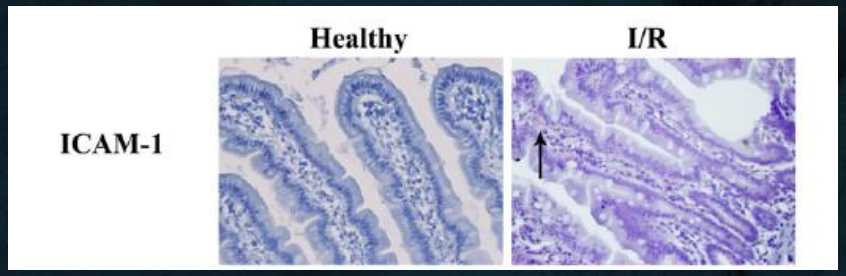
Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011

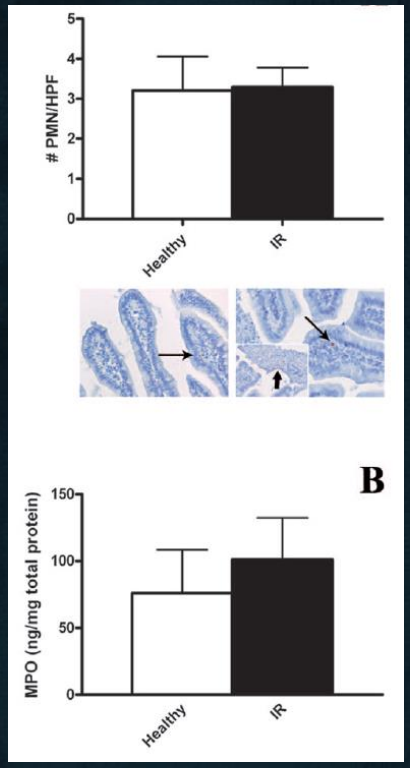
Zipper-like constriction



Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011

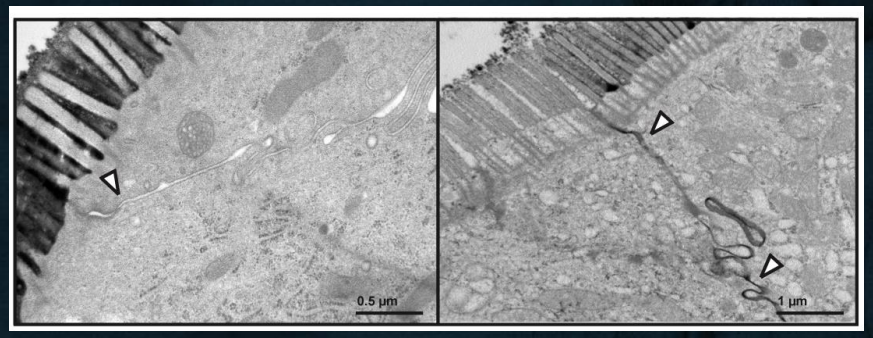
Short period of ischemia does not lead to inflammation

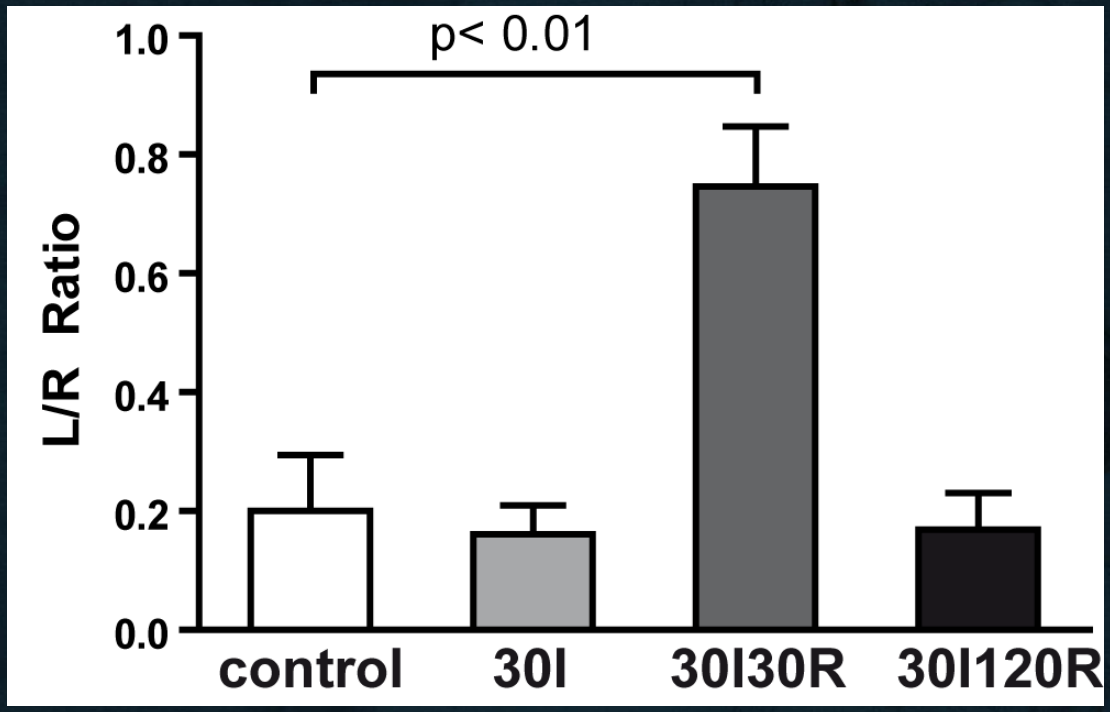




Matthijsen, Derikx et al. Plos One 2008

Short period of ischemia leads to reversible functional damage

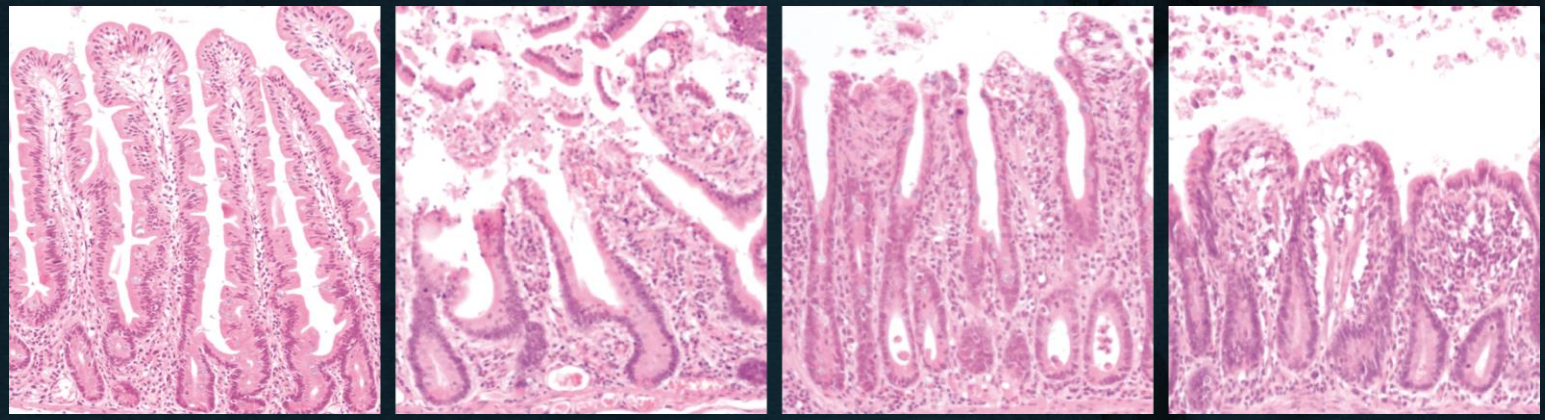


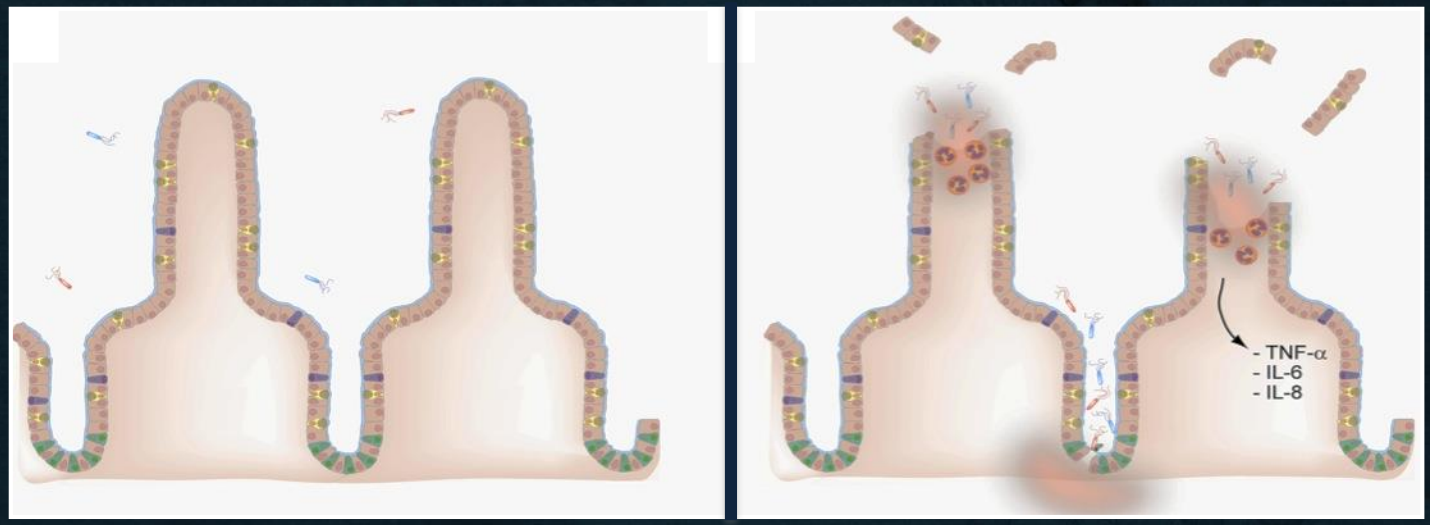


Schellekens, Derikx et al. WJG 2017

Long period of ischemia leads to irreversible damage

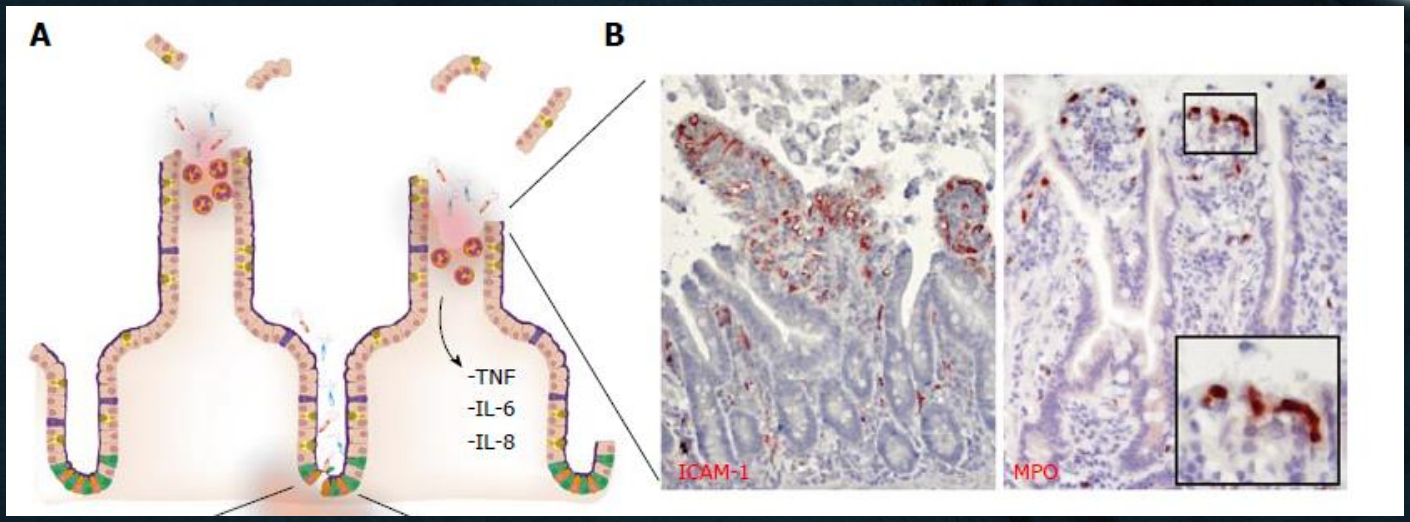
Control | 60I | 60I 30R | 60I 120R





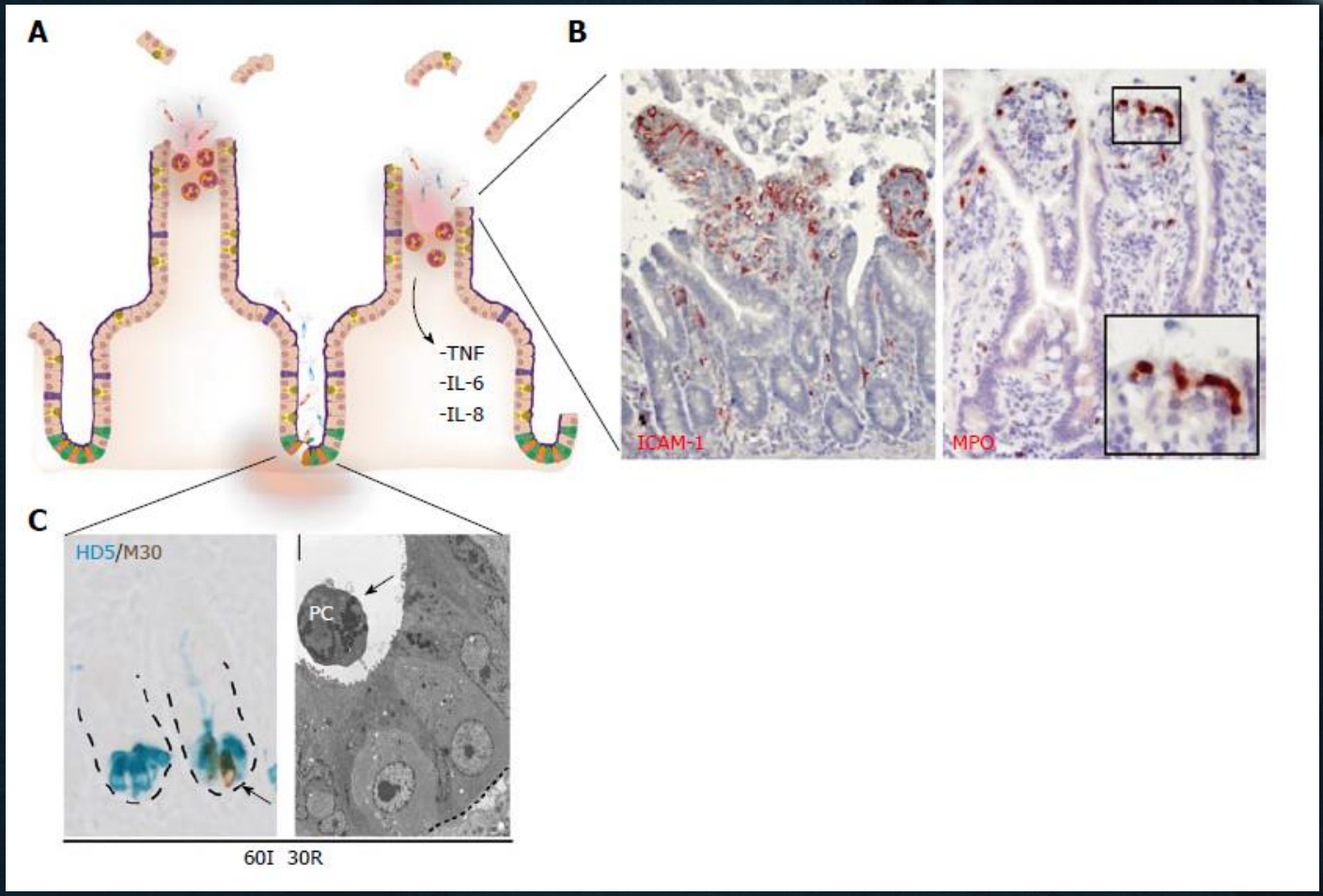
Grootjans, Derikx et al. Gastroenterology 2011
Schellekens, Derikx et al. J Clin Gastro 2013

Long period of ischemia leads to inflammation



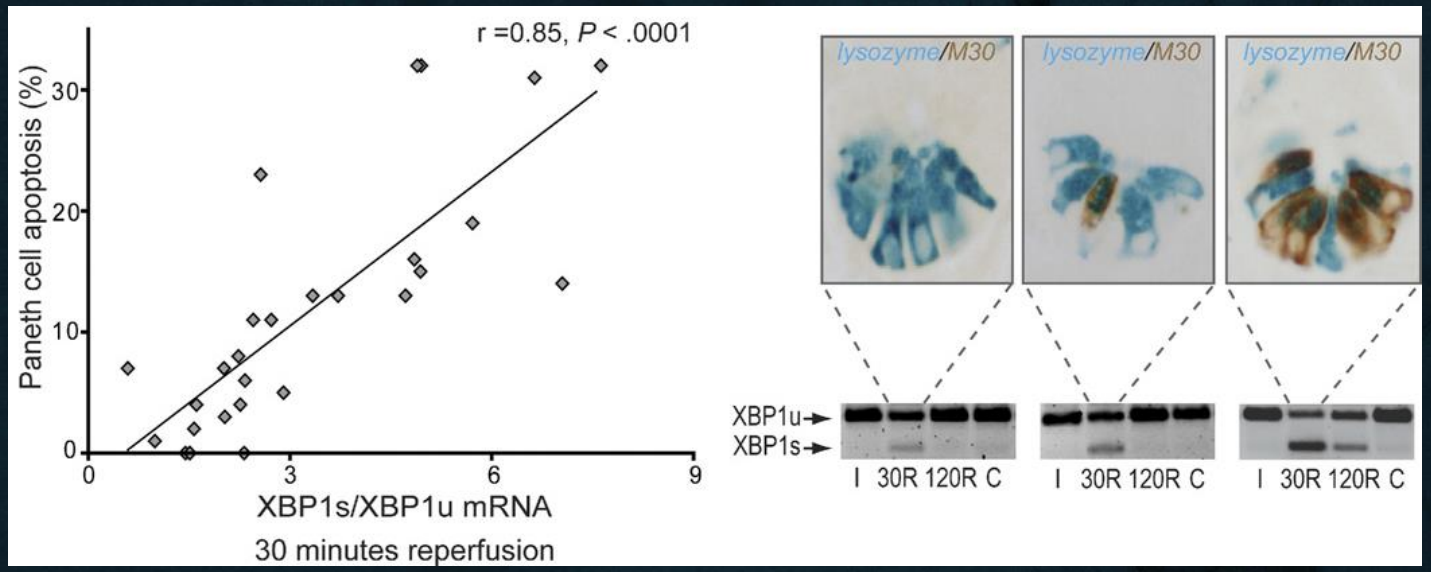
Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016

Long period of ischemia leads to inflammation and Paneth cell apoptosis



Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016

Long period of ischemia leads to Paneth cell apoptosis and ER Stress



Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016

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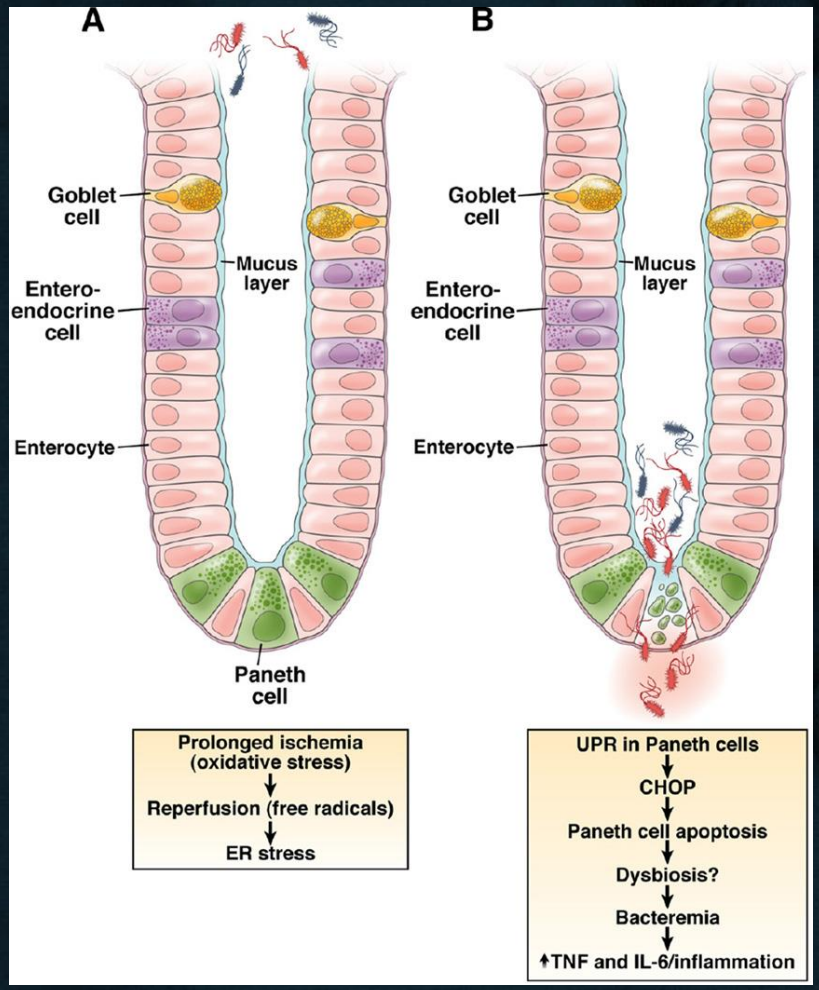
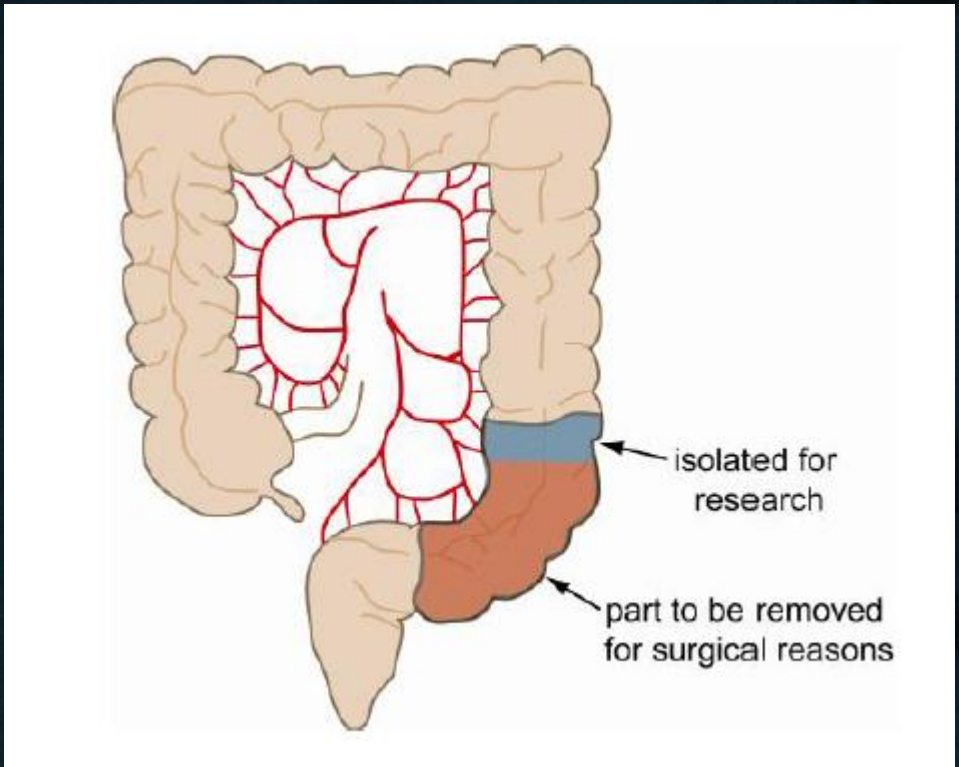


Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016

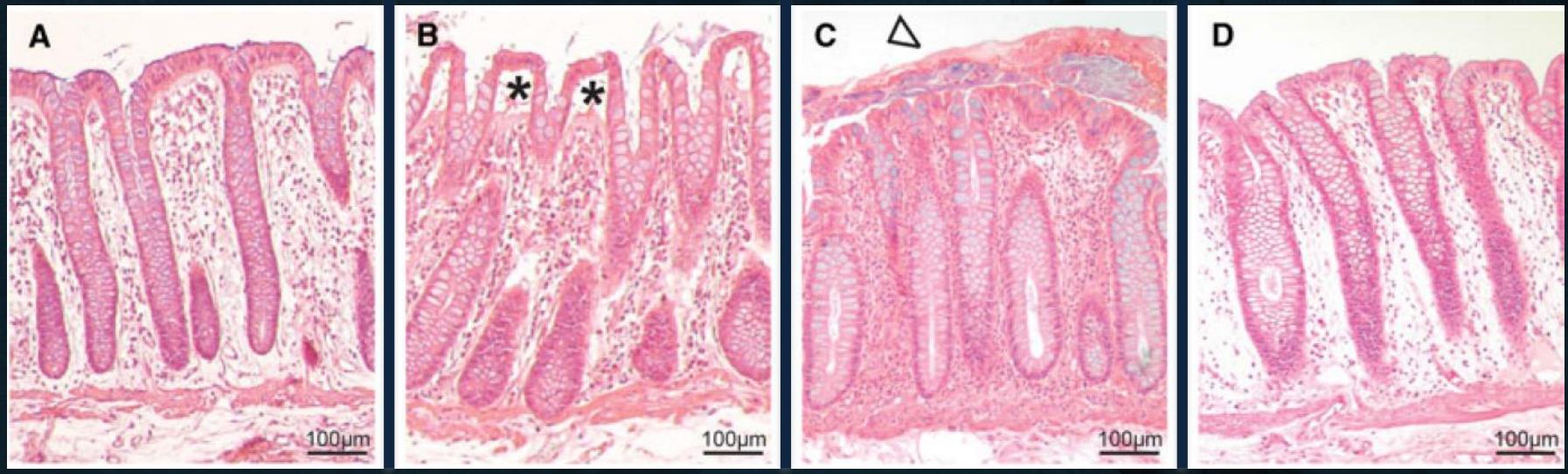
New model to study colon ischemia in man



Grootjans et al. Gut 2013
Hundscheid, Derikx et al. Ann Surg 2015

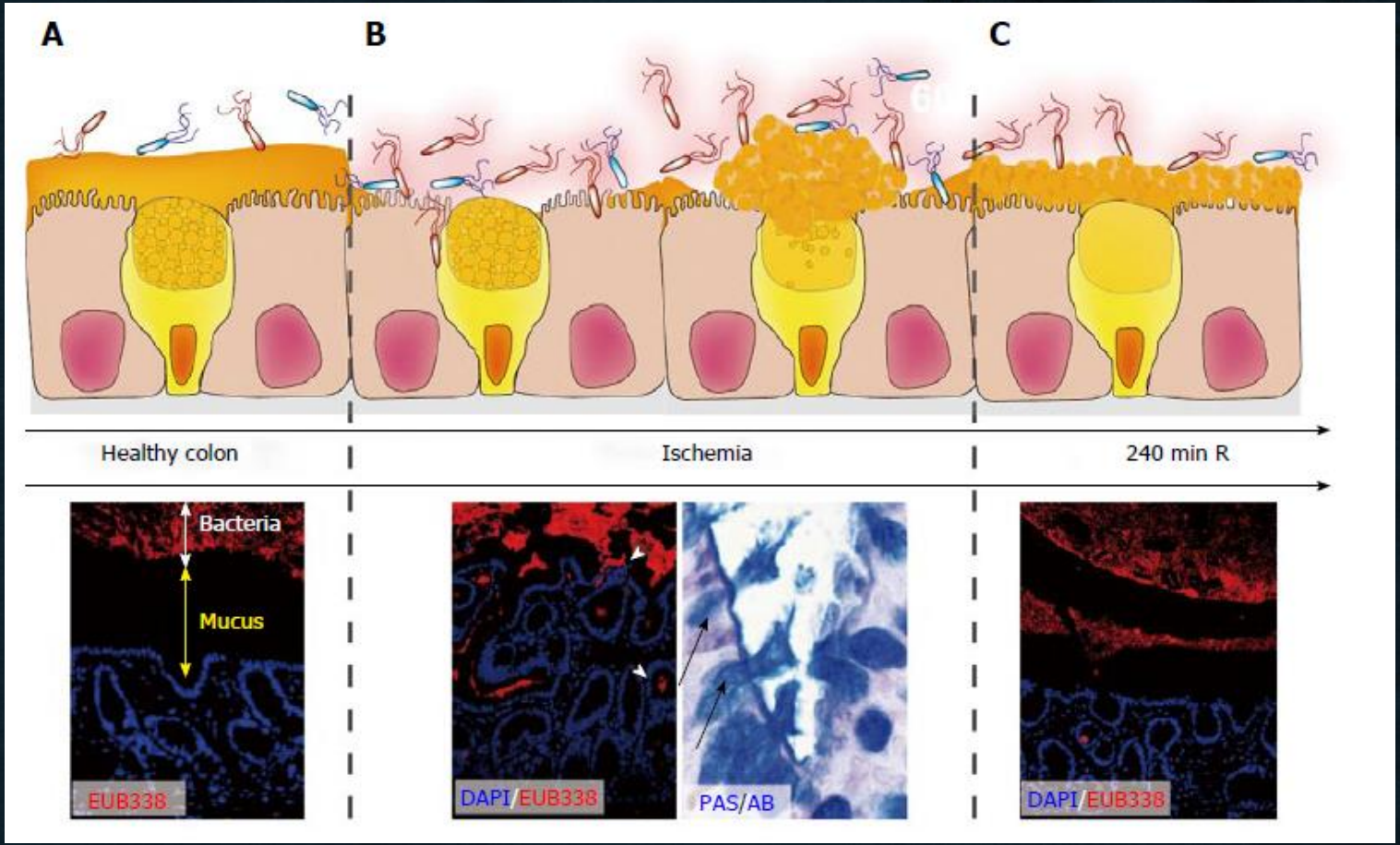
Short and long periods of colon ischemia lead to reversible damage

Control | 60I | 60I 30R | 60I 60R



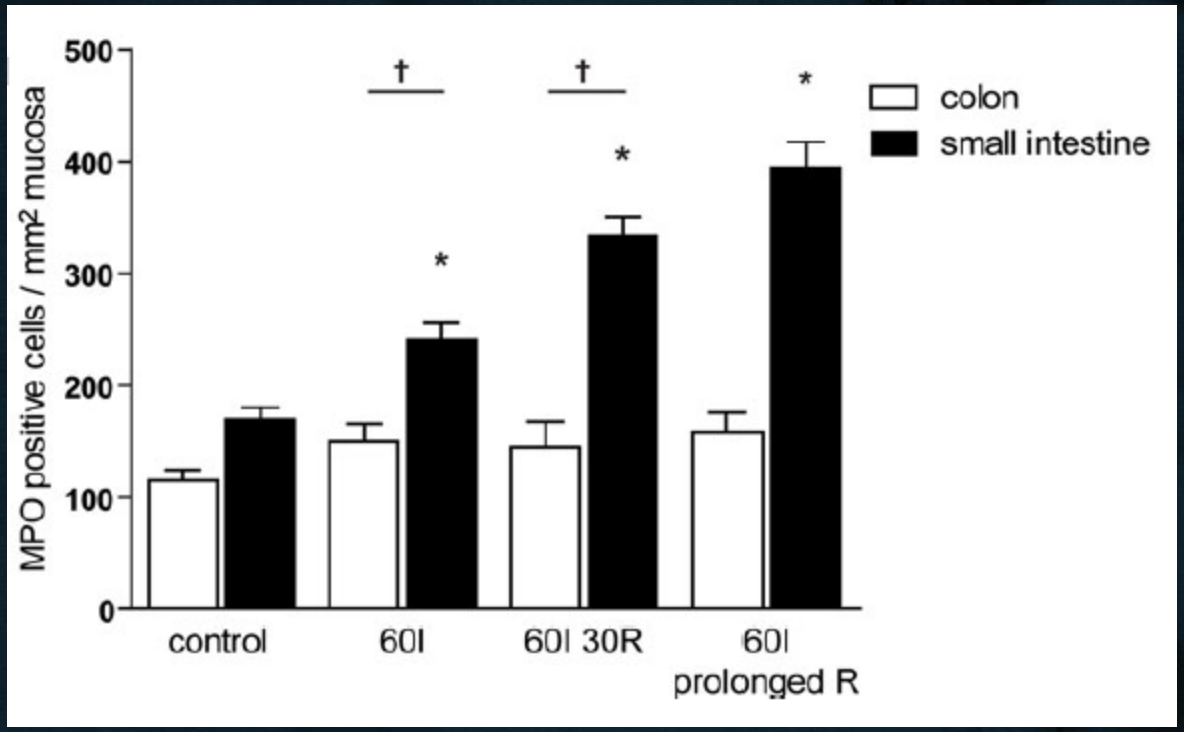
Grootjans et al. Gut 2013
Hundscheid, Derikx et al. Ann Surg 2015

Compound exocytosis



Grootjans et al. Gut 2013
Hundscheid, Derikx et al. Ann Surg 2015

Short and long periods of colon ischemia do not lead to inflammation

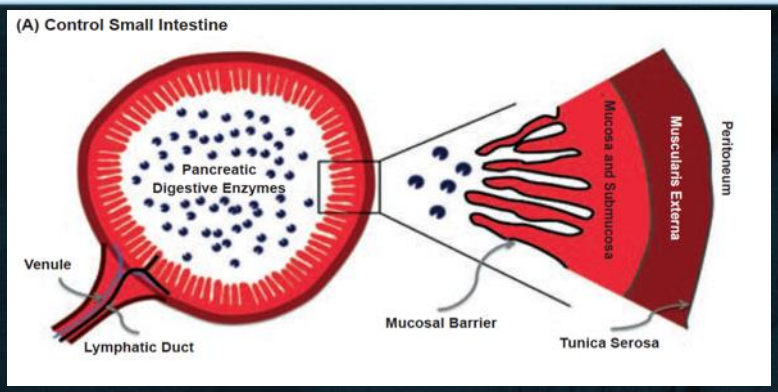


Hundscheid, Derikx et al. Ann Surg 2015

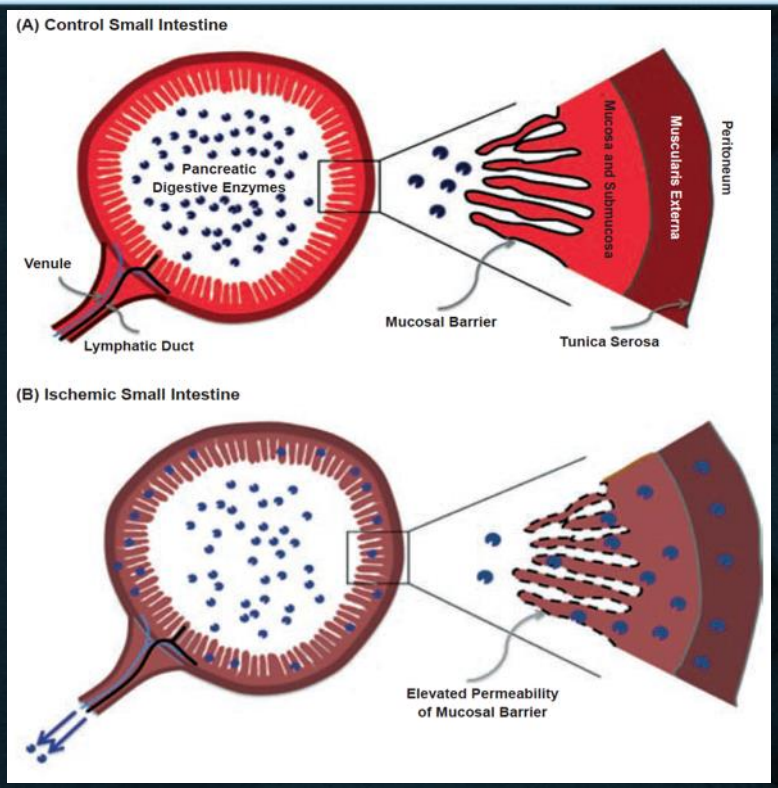
Current research

1. What causes the sequelae of intestinal ischemia?
2. How to prevent it?

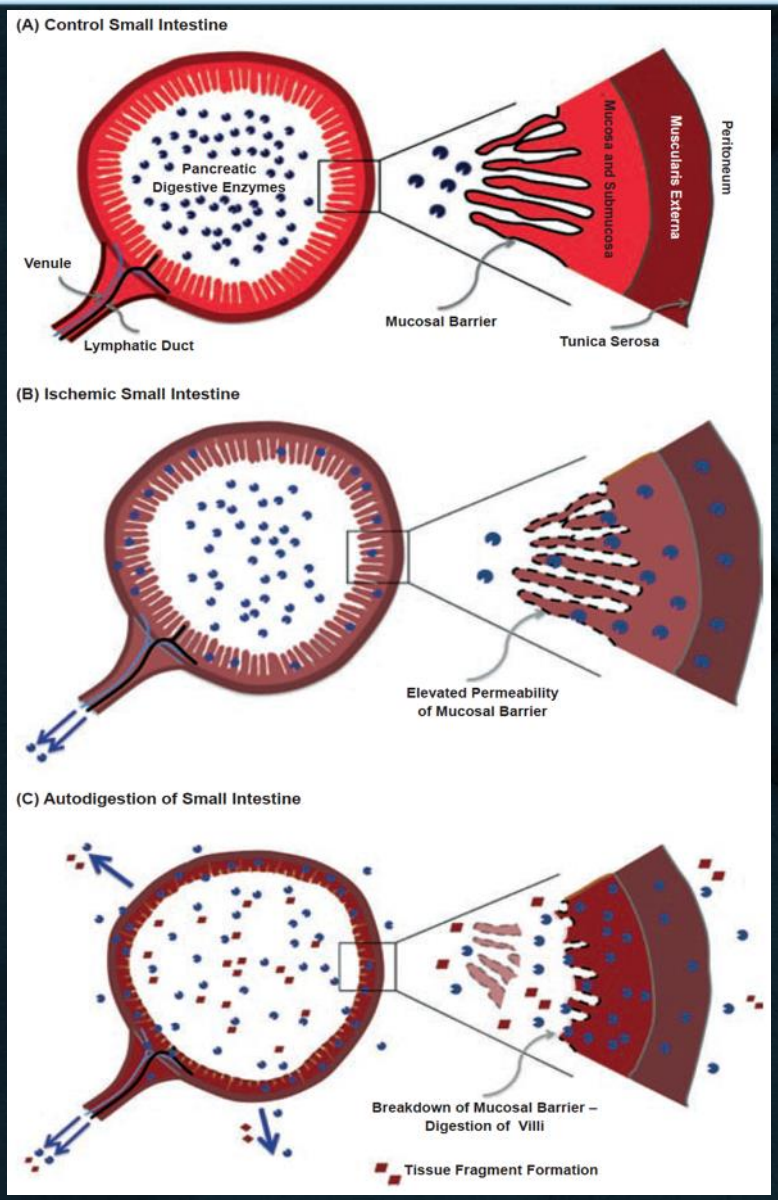
Role of proteases: normal intestine



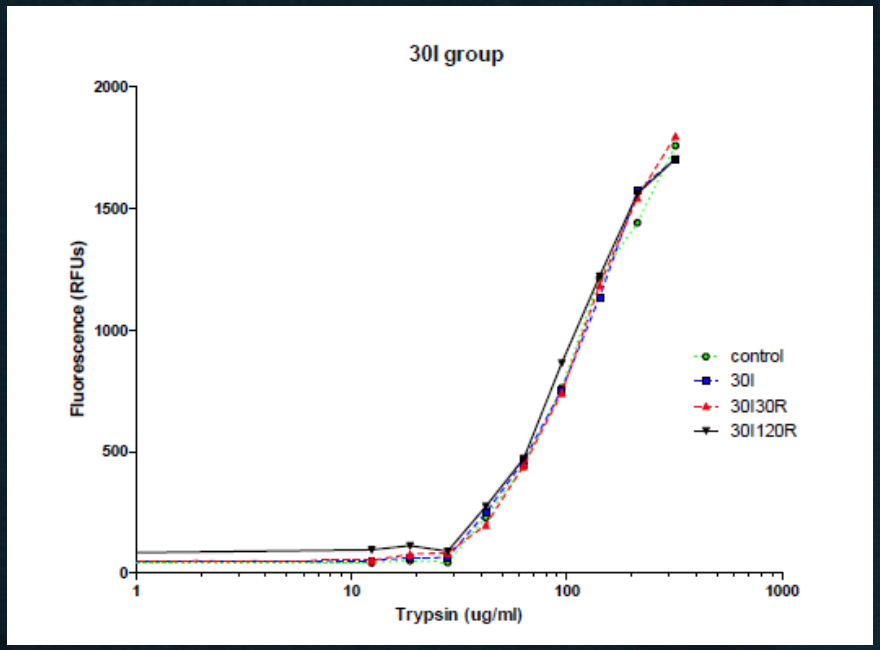
Role of proteases: intestinal ischemia

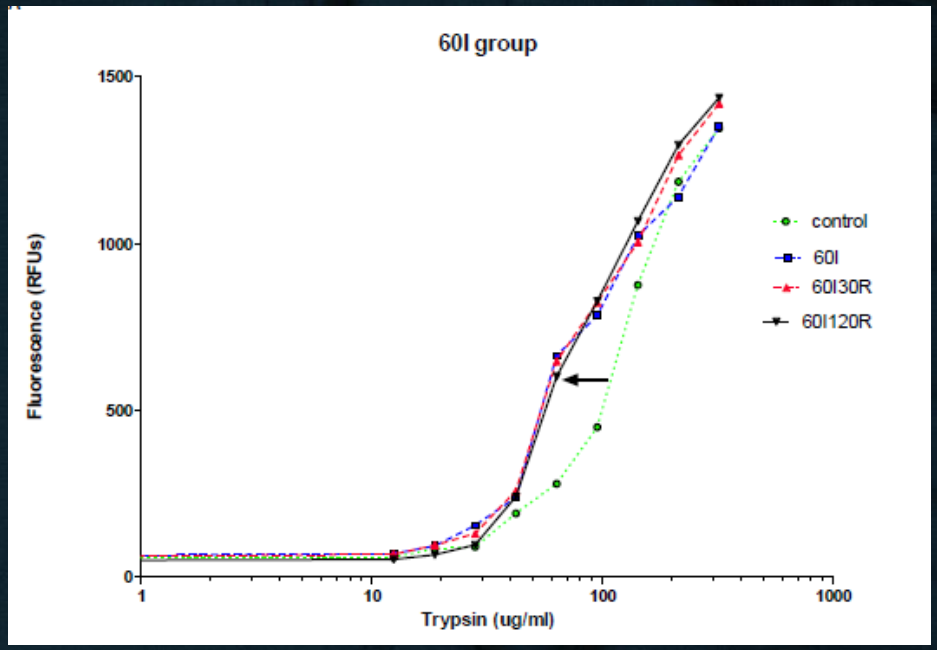


Role of proteases: autodigestion



Trypsin activity is increased after long period of jejunal ischemia



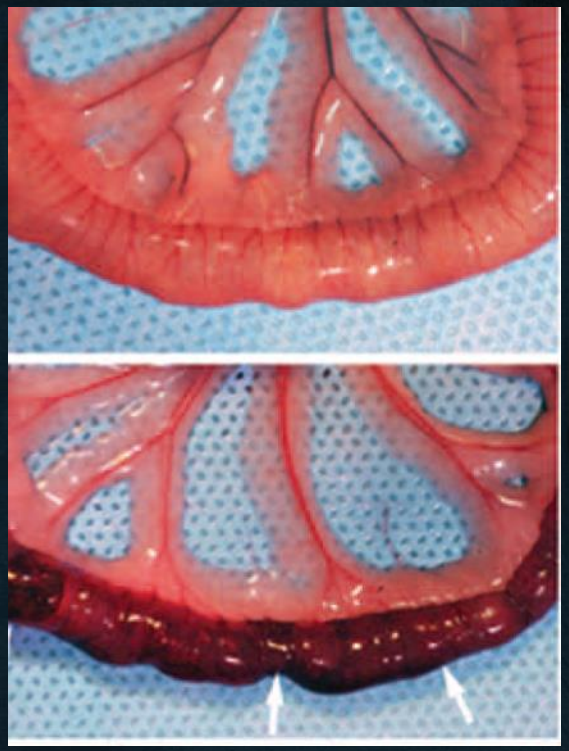


Leenarts, Derikx et al. Submitted

Proteases are crucial during intestinal ischemia in animals

Control

Intestinal ischemia

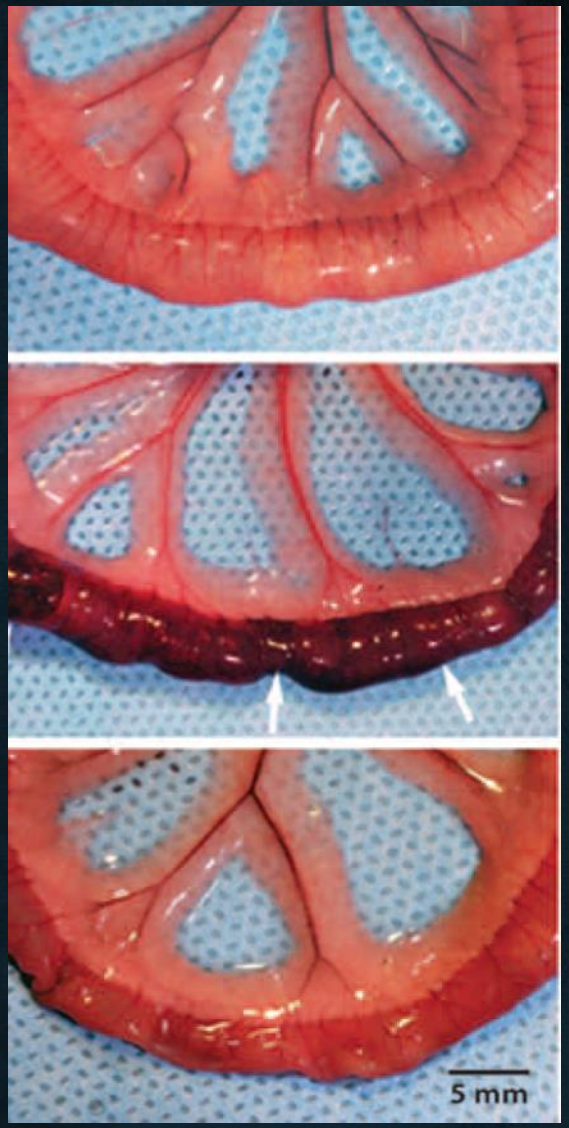


Proteases are crucial during intestinal ischemia in animals

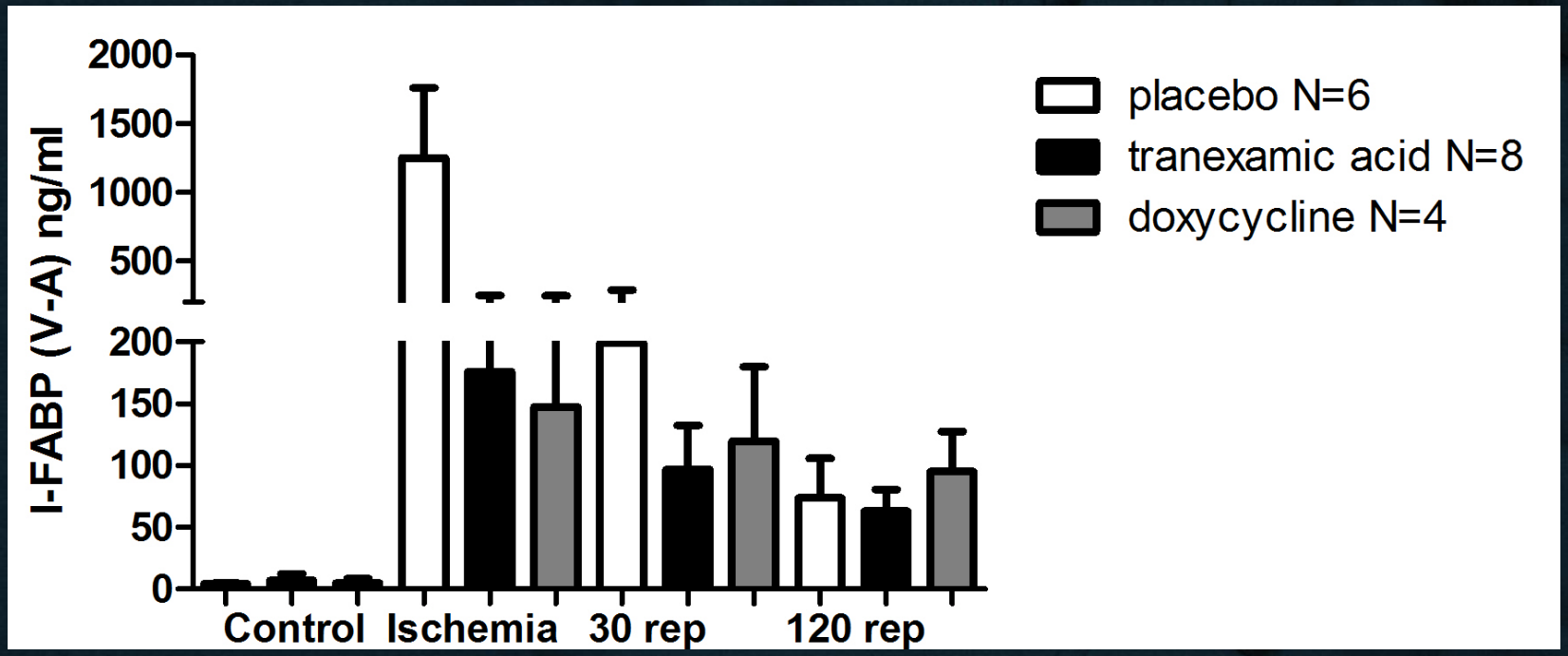
Control

Intestinal ischemia

Intestinal ischemia + protease-inhibitors



Protease inhibition leads to less mucosal cell damage in long jejunal IR



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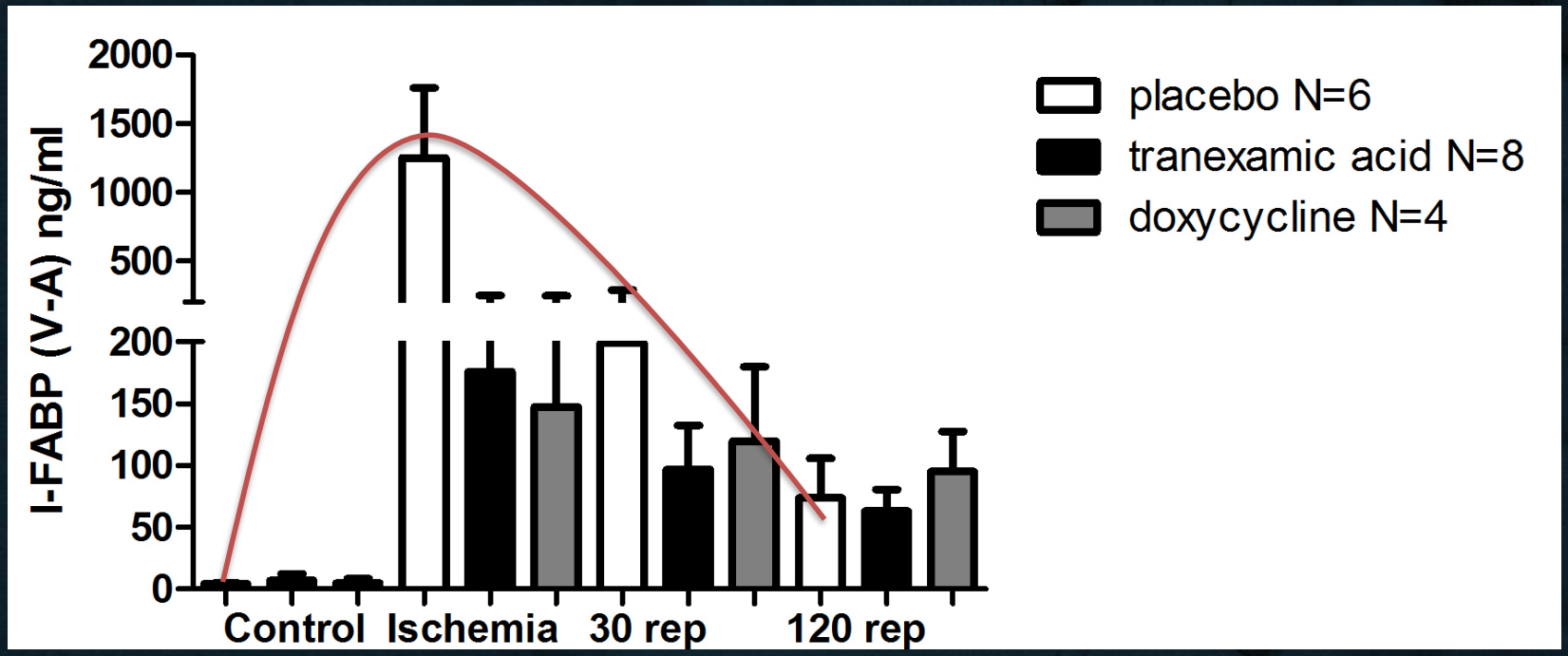

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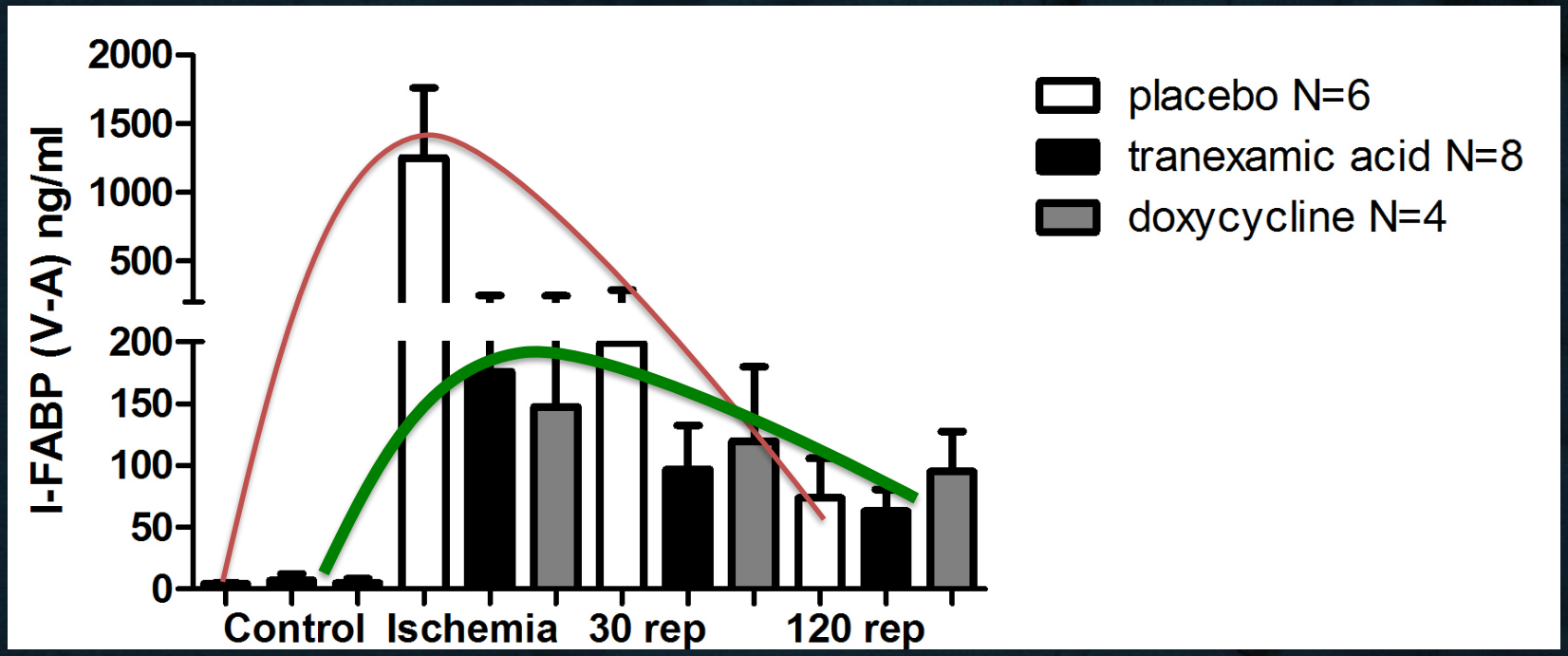
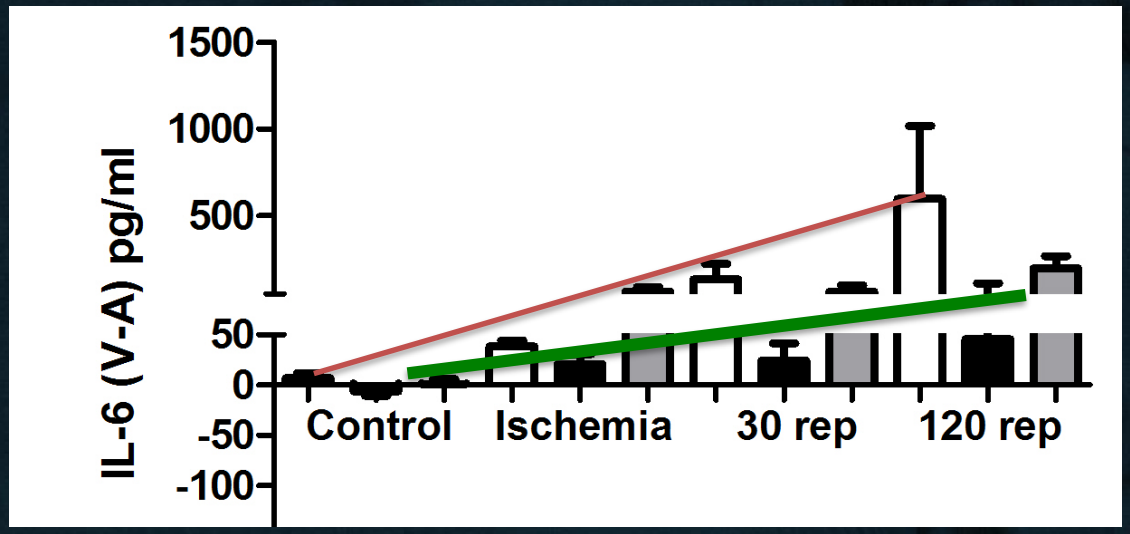
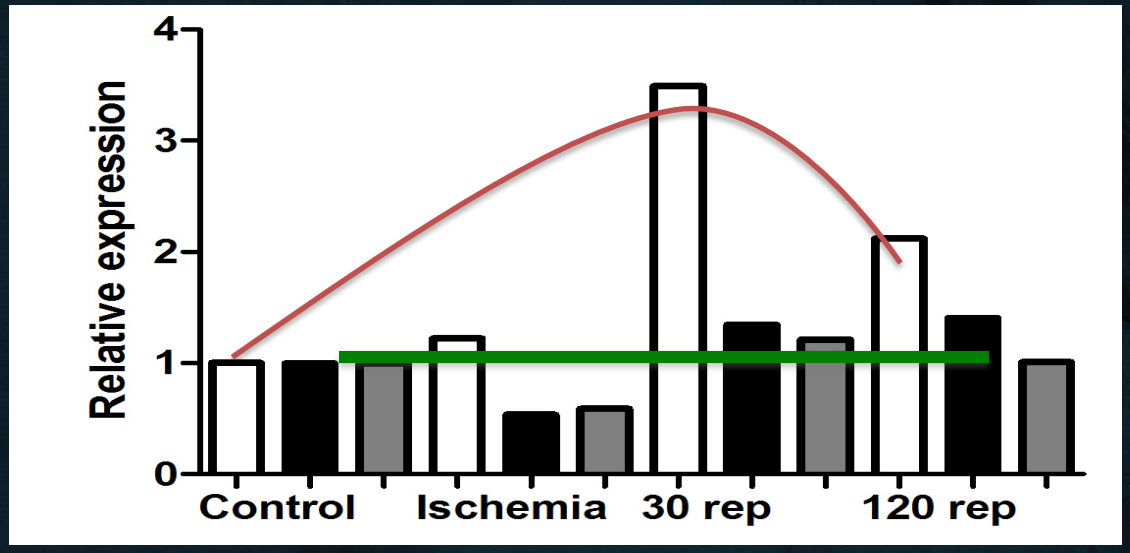


Protease inhibition leads to less inflammation in long jejunal IR



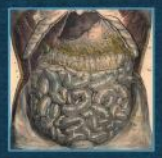


Conclusion

- Short jejunal ischemia leads to reversible damage
  - ➔ zipper-like constriction
- Long jejunal ischemia leads to irreversible damage
  - ➔ Paneth cell apoptosis
- Long colon ischemia leads to reversible damage
  - ➔ compound exocytosis mucus
- The role of proteases as mediators of autodigestion

Thank you…

Wim Buurman



Dirk Schellekens

Inca Hundscheid

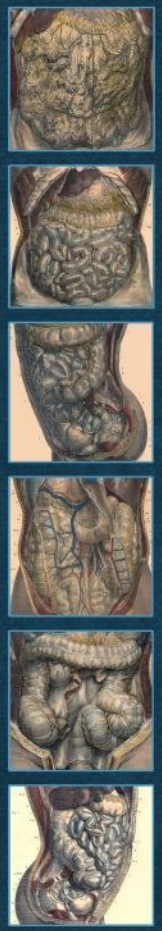
Claire Leenarts

Kaatje Lenaerts

Joep Grootjans

Kees de Jong

Thank you for your attention



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Amsterdam

Protective mechanisms