Putative function of goblet cells as epithelial sealing in ischaemia/reperfusion-induced intestinal barrier dysfunction

We read with great interest the article by Michael Camilleri who described in detail the important functions of goblet cells and the mucus component for intestinal barrier function.[1] Apart from diseases resulting in intestinal inflammation and damage, intestinal ischaemia/reperfusion (I/R) injury also leads to epithelial cell damage, release of epithelial cells into the luminal space and as a consequence reduced barrier function.[2–4] The latter enables bacterial translocation and in its severest form results in systemic inflammation and organ dysfunction.[5] The fundamental importance of goblet cell secretory products in restricting bacterial translocation has also been reported previously in *Gut* by Grootjans *et al* who showed that colonic ischaemia leads to disruption of the mucus layer facilitating bacterial penetration into the underlying tissue and that this process is counteracted by

increased secretory activity of goblet cells.[6]

We are currently performing a clinical trial in which the effects of remote ischaemic preconditioning on intestinal I/R damage are investigated. In our study which involves male and female patients undergoing pancreatoduodenectomy (Whipple procedure, n=30 patients, Ethics approval number: D471/17—Ethics Committee of the Christian-Albrechts-University, Kiel, Germany) a small part of the intestine, which has to be removed for surgical reasons, is exposed to 30 or 60 min of ischaemia followed by 30 min of reperfusion (figure 1A). Our preliminary findings of the ongoing trial are so far in line with the results of the above-mentioned studies; however, data retrieved from tissue sections suggested an additional considerable increase in the numbers of goblet cells at the villus tip after I/R when compared with the tissue samples before I/R (figure 1B).

These tentative results from our clinical study encouraged us to investigate in more detail the effects of I/R on the intestinal epithelium using our established isolated perfused model of the rat/mouse small intestine that provides detailed insights into the physiology of the small intestine and allows us to study fundamental processes such as fluid homeostasis, barrier functions, transport mechanisms and immune responses (figure 1C).[7] Using n=6 animals per group and analysing 100 villi per animal, we detected a significant increase in the numbers of villi containing ≥50% goblet cells at the villus tip after intestinal I/R injury (60 min ischaemia and 30 min reperfusion) compared with the control group (0.93±0.05 vs 0.06±0.03, p<0.001; figure 1D,E). Goblet cell accumulation was mainly confined to the villus tip and the cells contained abundant amounts of mucus (figure 1D). In addition, measurements of intraluminal lactate dehydrogenase (LDH) levels as a marker of cell damage[8] revealed high amounts of LDH/mg dry weight in the I/R group, while LDH levels in the control group were low (481.40±186.20 vs 98.52±125.00, p<0.01; figure 1F). These findings suggest that I/R leads to damage and loss of epithelial cells (results of luminal LDH measurements) and that epithelial gaps, which are the consequence of I/R mediated loss of epithelial cells, may be filled by existing goblet cells via directed migration (results of histological and morphometric analyses).

Taken together, in addition to the already described increased release of mucus and goblet cell-specific products during and after I/R, our data suggest an even more profound role of this cell type: goblet cells may be more resistant against I/R injury than other cells of the intestinal epithelium and could exert an unique protective function by migrating into damaged areas, thereby 'sealing' intraepithelial I/R-induced gaps.

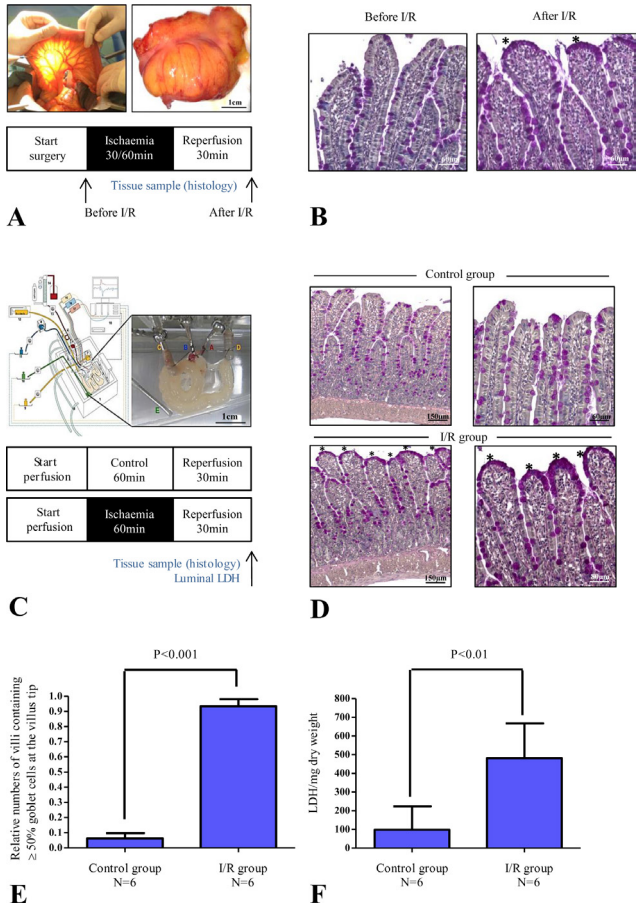

Figure 1 (A) Experimental protocol of the clinical trial. (B) Histology (periodic acid-Schiff (PAS) staining) of human intestinal tissue samples. (C) Isolated perfused model of the rat small intestine. (A) (red), arterial cannula; (B) (blue), venous cannula; (C) (yellow), luminal cannula (oral); (D) (yellow), luminal cannula (aboral); (E) (green), lymphatic suction needle. (D) Histology (PAS staining) of rat intestinal tissue samples. (E) Evaluation of numbers of villi containing ≥50% goblet cells at the villus tip. (F) Quantification of luminal LDH. Columns show the mean, bars denote SD. Kolmogorov-Smirnov normality tests and Student's t-tests (two-tailed) were employed. Asterisks (*) denote villi with goblet cell accumulations at the tip. I/R, ischaemia/reperfusion; LDH, lactate dehydrogenase.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Wong YL, Hummitzsch L, Lautenschläger I, *et al*. *Gut* 2020;**69**:1888–1890.

Received 2 September 2019
Revised 4 October 2019
Accepted 9 October 2019
Published Online First 30 October 2019

Gut 2020;**69**:1888–1890. doi:10.1136/gutjnl-2019-319770

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REFERENCES

1 Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. *Gut* 2019;68:1516–26.
2 Grootjans J, Lenaerts K, Buurman WA, *et al*. Life and death at the mucosal-luminal interface: new perspectives on human intestinal ischemia-reperfusion. *World J Gastroenterol* 2016;22:2760–70.
3 David H, Siems WG, Ellermann J. Ultrastructure and biochemistry of ischemic damages of small intestinal epithelial cells. *Exp Toxicol Pathol* 1992;44:325–35.
4 Chiu CJ, McArdle AH, Brown R, *et al*. Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. *Arch Surg* 1970;101:478–83.
5 Piton G, Capellier G. Biomarkers of gut barrier failure in the ICU. *Curr Opin Crit Care* 2016;22:1–60.
6 Grootjans J, Hundscheid IHR, Lenaerts K, *et al*. Ischaemia-Induced mucus barrier loss and bacterial penetration are rapidly counteracted by increased goblet cell secretory activity in human and rat colon. *Gut* 2013;62:250–8.
7 Lautenschläger I, Dombrowsky H, Frerichs I, *et al*. A model of the isolated perfused rat small intestine. *Am J Physiol Gastrointest Liver Physiol* 2010;298:G304–13.
8 Kumar P, Nagarajan A, Uchil PD. Analysis of cell viability by the lactate dehydrogenase assay. *Cold Spring Harb Protoc* 2018;2018:pdb.prot095497.