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MICROBIOTA DYSBIOSIS INDUCED BY DEFECT OF PANETH CELLS TRIGGERS VISCERAL HYPERSENSITIVITY IN MICE

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Background and objective: Paneth cells are an important player in innate immunity. They contribute to the appropriate colonization with commensal bacterial by secreting antimicrobial compounds. Defect in Paneth cell numbers and/or antimicrobial activity has been incriminated in susceptibility to Crohn's disease (CD). Despite high discrepancies concerning the severity of intestinal inflammation between CD and Irritable Bowel Syndrome (IBS) some common pathophysiological features such as visceral hypersensitivity and microbiota dysbiosis have been reported. Interestingly, among environmental factors affecting the course of these diseases, early life adverse events play a crucial role. Indeed, MS performed in rat decreases epithelial secretory cell lineages including that is associated with visceral hypersensitivity. However, a mechanistic link between Paneth cells defect and visceral hypersensitivity has never been investigated. In this study, we aimed at developing a MS mouse model and deciphering the mechanisms responsible for visceral hypersensitivity at adulthood.

Design / results: MS in mice reproduced rat's observations i.e. visceral hypersensitivity and defect of Paneth cell. In our model, Paneth cell defect was associated with a decrease of faecal antimicrobial activity. To assess the potential role of Paneth cells in visceral sensitivity, Sox9^{flox/flox}-vil-cre mice deficient for Paneth cell were used. In 50-days old Sox9^{flox/flox}-vil-Cre mice, the absence of Paneth cells was associated with visceral hypersensitivity mimicking our previous observation with MS mice. Both MS and Sox9^{flox/flox}-vil-Cre mice displayed faecal dysbiosis. By comparing faecal microbiota alterations in these two mouse models, we observed that *E. coli* expansion was an important common contributor. Furthermore, daily gavage of conventional adult mice with 10⁹ commensal *E. coli* was sufficient to induced visceral hypersensitivity. Conversely, daily oral administration of lysozyme prevented MS-induced antimicrobial defect leading to *E. coli* expansion and its consequences on visceral sensitivity.

Conclusion: Altogether our results show that a defect in enteric antimicrobial functions leads to abnormal *E. coli* expansion responsible for visceral hypersensitivity. Thus providing new mechanistic insights in maternal separation-induced visceral hypersensitivity and highlighting Paneth cells role in visceral sensitivity that might be worthwhile to investigate in IBS.