Pro-Inflammatory Role of Bone Morphogenetic Protein 2 in Acute Pancreatitis in Aged mice

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Introduction

Susceptibility of acute pancreatitis (AP) increases with aging in human [1]. However, the underlying mechanisms are not well defined. Bone morphogenetic protein (BMP) signaling pathway is a pathway that directs differentiation, maintains stem cell niches, coordinates cellular response to injury, and influences many disease processes, including inflammation [2]. We previously reported that in young mice, BMP signaling is upregulated in cerulein-induced AP: AP injury can be attenuated by a BMP antagonist, noggin, suggesting a pro-inflammatory role of BMP signaling [3]. In this study, we explored role of BMP signaling in aging-related AP-induced inflammation. The goal is to uncover the fundamental mechanisms contributing to aging-related AP and ultimately develop strategies to reduce AP morbidity and mortality in aging population.

Objective

To investigate the role of BMP signaling in AP in aged mice by comparing young mice in a cerulein-induced AP model.

Methods

AP was induced in young (4m) and aged (24m) male C57BL/6 mice by cerulein (50μg/kg, 9 hourly ip injections); control mice received PBS (n=2 mice/group). An additional set of AP mice received Noggin. The mice were euthanized 1h after the last injection, the blood was harvested for analysis of serum cytokines, amylase and lipase; the pancreas was harvested for AP score, cyclooxygenase (COX2) protein expression by western blotting (WB). Primary pancreatic acini were isolated and treated with BMPs (1.6μM for 24h); the cell lysates were prepared for COX2 protein expression.

Results

1. Serum levels of proinflammatory cytokines levels and pancreatic levels of COX2 protein increase dramatically in aged mice compared to young mice in a cerulein-induced AP model

In vitro AP model

- Bar100um

2. Aged acinar cells have remarkably higher basal and BMP2-induced COX2 protein expression

In vitro acinar cell model

- kD

- V

- B2

- B4

- B7

- COX2

- β-actin

3. Aged mice demonstrate lower AP scores and serum levels of pancreatic enzymes, and are resistant to in vivo Noggin administration in the cerulein-induced AP, compared to young mice.

Fig. 1 Cerulein-induced AP injury in aged mice compared to young mice. C57BL/6 mice, young (4m) and aged (24m), were used for cerulein-induced AP (male, n=2 mice/group). A. Representative H&E images of the pancreatic sections. B. Serum levels of IL-6, BMP2, and TGF-β1 detected by ELISA. C. COX2 protein levels detected by WB. *p<0.05 compared with CON (control). *p<0.05 compared with young AP.

Fig. 2. Induction of COX-2 protein expression in pancreatic acinar cells in response to BMP2 in vitro. Primary acinar cells were isolated and treated with vehicle (V), and BMP2, BMP2 (B2), BMP4 (B4), BMP7 (B7) for 24h. Cell lysates were prepared for WB.

Fig. 3. Different AP injury patterns and responses to in vivo Noggin administration in aged and young mice. AP was induced by cerulein. CON received PBS. An additional set of AP mice received Noggin (Nog, 1 mg/kg) 1h prior to AP induction. AP score, serum levels of amylase and lipase, serum levels of IL-6, BMP2, and TGF-β1 are measured and analyzed. *p<0.05 compared with CON, *p<0.05 compared with AP.

Conclusions

We observe dramatically increased basal and AP-induced systemic inflammation in aged mice compared to young mice; and enhanced BMP2-induced inflammatory response in vivo in aged acinar cells.

Increased BMP2 levels in vivo in aged mice and enhanced BMP2-induced inflammatory response in vitro in aged acinar cells suggest that BMP2 may play a pro-inflammatory role in aging-related AP-induced inflammation.

Extra caution should be taken for AP evaluation in aging due to observation of the atypical or potentially delayed pancreatic injury patterns in aged mice, compared to young mice.

References


Acknowledgments

We thank Qiajin Li at Department of Surgery and Histology Laboratory at Department of Pathology and Laboratory Medicine, UTHealth for technical support. This study was supported by 1R21AA0207014-01A1, Jack H Mayfield M.D. Distinguished Professorship in Surgery, and UTHealth MMS pilot grant 2021 (T.C.K.).