PhD:
Medicine

Name of Student:
Henrique Baptista Sobral do Rosário

Subject of Thesis:
Matrix matelloproteinase-9 and pancreatic trypsin in the intestinal wall – A contribution to the understanding of intestinal ischemia-reperfusion

Area:
Medicine

Specialty:
Biochemistry

Date of Defence:
18/07/09

Mark:
Approved with Distinction and Praise by Majority

Jury:
Presided over by the President of the Scientific Council of the FMUL, Professor Henrique Bicha Castelo, and present were the following jury members: Professors G. Schmid- Schonbein, from the University of California, Catarina Resende de Oliveira, from the University of Coimbra, João Martins e Silva, Miguel Augusto Rico Botas Castanho, José Manuel Fernandes e Fernandes, Rui Victorino and Carlota Saldanha Lopes, all from the University of Lisbon.

ABSTRACT

Ischemia-reperfusion of the intestine produces a set of inflammatory mediators, the origin of which has recently been shown to involve pancreatic digestive enzymes. Matrix metalloproteinase-9 (MMP-9) participates in a variety of inflammatory processes including myocardial, hepatic, and pancreatic ischemia-reperfusion. In the present study, we explore the role of neutrophil- derived MMP-9 in acute intestinal ischemia-reperfusion and its interaction with pancreatic trypsin. Male Sprague-Dawley rats were subjected to 45 minutes of superior mesenteric arterial occlusion followed by 90 minutes of reperfusion. *In situ* zymography of the proximal jejunum reveals increased gelatinase activity in the intestinal wall after ischemia-reperfusion. Gel electrophoresis zymography and immunofluorescence co-localization suggests that this gelatinase activity is derived from MMP-9 released from infiltrating neutrophils. The role of intraluminal trypsin in this process was investigated using an *in vivo* isolated jejunal loop model of intestinal ischemia-reperfusion. Trypsin increased the inflammatory response after reperfusion, with an augmented neutrophil infiltration of the intestinal wall. Furthermore, trypsin stimulated a rapid conversion of neutrophil-released proMMP-9 into the lower molecular weight enzymatically active MMP-9. This process represents a powerful *in vivo* pathophysiological mechanism for trypsin-induced MMP-9 activation and is likely to play a central role in the development of acute intestinal inflammation and shock.