Mice lacking the transcription factor Mist1 exhibit an altered stress response and increased sensitivity to caerulein-induced pancreatitis.

C.L. Johnson
Abstract

Several animal models have been developed to investigate the pathobiology of pancreatitis, but few studies have examined the effects that altered pancreatic gene expression have in these models. In this study, the sensitivity to secretagogue-induced pancreatitis was examined in a mouse line that has an altered acinar cell environment due to the targeted deletion of Mist1. Mist1 is an exocrine specific transcription factor important for the complete differentiation and function of pancreatic acinar cells. Mice lacking the Mist1 gene [Mist1 knockout (KO) mice] exhibit cellular disorganization and functional defects in the exocrine pancreas but no gross morphological defects.

Discussion

Link of Mist1 to the disease process

It is unclear if the CIP effects observed in Mist1 KO mice are due to the specific loss of Mist1 transcriptional activity or due to the development of a more susceptible
environment in its absence. Deletion of Mist1 results in abnormal acinar cell organization, gene expression, and function. However, Mist1 KO mice are viable, fertile, and indistinguishable from WT littermates at a gross morphological level.\textsuperscript{43} To date, it has been difficult to establish a molecular hierarchy by which the loss of Mist1 leads to exocrine cell defects. This is probably due to fact that Mist1 regulates a number of exocrine-specific genes that affect numerous cellular functions.\textsuperscript{23, 43, 44} Our array analysis has revealed a large number of genes that are differentially expressed between WT and Mist1 KO pancreatic tissue, but likely these changes represent a combination of direct targets of Mist1 as well as the consequences of an altered pancreatic environment. Regardless of how the loss of Mist1 leads to the pancreatic phenotypes observed in Mist1 KO mice, these mice still respond to pancreatitis in a dramatically different way at the molecular level compared with WT mice (Tables 3 and 4). It is possible that these changes are directly due to an absence in Mist1 transcriptional activity in Mist1 KO mice. However, it is likely that the altered acinar and pancreatic environments that exist in Mist1 KO mice also contribute to disease severity. For example, Mist1 KO pancreatic tissue has increased numbers of stellate cells that are activated during the early stages of pancreatitis and promote the fibrosis that is associated with the disease.\textsuperscript{43} In addition, even though Mist1 is expressed exclusively in the exocrine pancreas, work from our laboratory\textsuperscript{10} has indicated that older Mist1 KO mice develop a reduced tolerance to elevated glucose levels, likely due to specific effects on the endocrine tissue. …
References

For one CSE model (citation-name system), sources are listed in alphabetical order by the author’s last name; in-text notes match the numbers of the reference list.


