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How the ACE2 protein is critical in the damage done to the insulin-producing cells of the pancreas

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The detailed mechanism of how SARS-CoV-2 attacks the insulin-producing cells of the pancreas by targeting the angiotensin converting enzyme 2 (ACE2) protein on the surface of those cells is the subject of a special presentation at this year's Annual Meeting of the European Association for the Study of Diabetes, given by Professor Francesco Dotta, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy.

"The SARS-CoV-2 virus attacks specific host tissues because of the presence of viral receptors on the surface of the target cells. As such, virus binding to ACE2 protein is the key determinant for its entry, propagation and transmissibility," explains Prof Dotta.

"Multiple studies have shown that older adults and those with chronic medical conditions like heart and lung disease and/or diabetes are at the highest risk for complications from SARS-CoV-2 infections. Moreover, impaired blood sugar control is associated with increased risk of severe COVID-19, suggesting a link between COVID-19 infection and diabetes. Several reports indicate a wide, although variable, distribution of the ACE2 protein among different tissues."

Prof Dotta's team and others have studied ACE2 expression pattern in pancreatic tissue samples of non-diabetic multiorgan donors in order to better understand the molecular link between COVID-19 and diabetes.

Particularly, their collaborative group analysed pancreatic tissue samples within the context of the INNODIA consortium, a large diabetes related research project funded by the EU, JDRF and Helmsely Foundation within the European IMI2 initiative.

In the 'normal' pancreas, ACE2 is highly expressed in microvasculature (tiny blood vessels) and in ductal cells (cells lining the connection between the pancreas and the bile duct). "Importantly, we found that ACE2 was expressed in human pancreatic islets, where it is preferentially expressed in insulin producing beta-cells. We also demonstrated that ACE2 levels were increased under pro-inflammatory conditions, thus confirming the link between inflammation and ACE2 also in pancreatic islet beta cells."

In order to correctly identify the mechanism involved in the upregulation of ACE2 induced by inflammation, ACE2 levels were measured in human pancreatic islets pre-treated with two drugs blocking inflammation in beta cells, namely Baricitinib or Nimbus (Jak1/2 and TYK2 inhibitors), and then exposed to pro-inflammatory conditions. Prof Dotta says: "We showed that these drugs prevent the ACE2 increase induced by inflammation in human pancreatic islets, demonstrating that SARS-CoV-2 receptor ACE2 is regulated through specific molecular pathways and that its increased expression can be prevented."

"In our collaborative work with the University of Pisa, University of Leuven and University of Brussels we studied the mechanisms of SARS-CoV-2 virus entry into insulin producing beta cells and we discovered that these cells express the SARS-CoV-2 receptor ACE2," concludes Prof Dotta. Such data have been independently confirmed by other authors.

Of note, additional published data confirmed that SARS-CoV-2 can

indeed infect pancreatic insulin-producing cells causing their dysfunction or death. Moreover, during inflammation the expression of SARS-CoV-2 receptor ACE2 increases of several times above standard values.

Prof Dotta concludes: "This means that these insulin-producing beta cells could be even more susceptible to viral infection when inflamed. This finding is also important from a clinical standpoint, since keeping inflammatory status under control in patients with COVID-19 may reduce the expression of ACE2 receptor in beta cells with beneficial effects on blood sugar and metabolic control of patients."

Provided by Diabetologia