When PDIA1 (aka DNAJB1) was subjected to metalloendocrinology modeling that encompassed the algorithm for quantum biology, the following factors were identified that can be verified by qualified bioinformatic professionals - DIY!

- PDIA1 has two other forms; i.e. PDIA2 and 3.
- Members of the PDIA family are correlated with PARP1 and DNAJB1
- Their amino acid constituents are glutamic acid - alanine/proline (a chirality issue) and glycine.
- An alternative designation relative to vascular repair can be verified as being DRP1 - 3. Refer to the following for links between PDIA and DRP relative to blood vessels: https://medicalxpress.com/news/2018-07-blood-vessel-diabetes.html

These facts provide the foundation for a testable theory that can lead reductions of CVD by ensuring the enzyme is part of cellular DNA defense mechanisms.

https://medicalxpress.com/news/2019-05-enzyme-predisposition-cardiovascular-disease.html

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Enzyme may indicate predisposition to cardiovascular disease

by FAPESP

Measuring the blood plasma levels of an enzyme called PDIA1 could one day become a method of diagnosing a person's predisposition to cardiovascular disease even if they are not obese, diabetic or a smoker, and with normal cholesterol.

This is suggested by a study published in the journal *Redox Biology* by Brazilian researchers affiliated with the University of São Paulo (USP), the University of Campinas (UNICAMP) and Butantan Institute.

The investigation was conducted under the aegis of the Center for Research on Redox Processes in Biomedicine (Redoxome), one of the Research, Innovation and Dissemination Centers (RIDCs) funded by the São Paulo Research Foundation (FAPESP). Redoxome is hosted by USP's Chemistry Institute.

"This molecule belongs to the protein disulfide isomerase [PDI] family. Our study showed that people with low plasma levels of PDIA1 have a more inflammatory protein profile and hence run a higher risk of thrombosis. On the other hand, people with high levels of PDIA1 have more 'housekeeping' proteins associated with cell adhesion, homeostasis and the organism's normal functioning," said Francisco Rafael Martins Laurindo, a professor at the University of São Paulo's Medical School (FM-USP) and principal investigator for the study.

The study was conducted during the Ph.D. research of Percíllia Victória Santos de Oliveira with a scholarship from FAPESP.

The group analyzed blood plasma samples from 35 healthy volunteers with no history of chronic or acute disease. None was a smoker or a user of recreational drugs or chronic medication.

Plasma was collected 10 to 15 times at intervals of days or weeks during a period of 10 to15 months. Circulating PDI levels were within a small range for most individuals. Moreover, in a cohort of five individuals, PDIA1 levels were measured three times in a nine-hour period. The variability of the results was again negligible.

"However, the measurements showed that some patients had high levels of PDIA1, while the levels were very low, almost undetectable, in others. When the tests were repeated for the same person over time, these values hardly varied at all," said Laurindo, who heads the Translational Cardiovascular Biology Laboratory at the Heart Institute (InCor) attached to FM-USP's teaching and general hospital (Hospital das Clínicas).

The researchers also measured the levels of PDIA1 in 90 plasma bank samples from patients with chronic cardiovascular disease. The analysis consistently showed low levels of the enzyme.

They then conducted several additional proteomic studies to investigate how the plasma levels of PDIA1 correlated with an individual's protein signature. The adhesion and migration of cultured vein endothelial cells treated with PDIA1-poor plasma were impaired in comparison with those of cells treated with PDIA1-rich plasma.

These results led to the hypothesis that the plasma level of PDIA1 could be a window onto individual plasma protein signatures associated with endothelial function, which could indicate a possible predisposition to cardiovascular disease. The study also showed no correlation between PDIA1 levels and well-known risk factors for cardiovascular disease, such as triglycerides and cholesterol.

The next steps for the research group include studying PDIA1 levels in conditions such as acute coronary disease, as well as other members of the protein disulfide isomerase family (there are more than 20 PDIs all told), to compare results and confirm whether all these enzymes are potential markers of vulnerability to cardiovascular disease.

Inhibitors

Clinical trials of inhibitors of other PDIs are being conducted by groups of researchers in several parts of the world. Because these enzymes play various essential roles in cell survival, Laurindo explained, it is important to understand their specific interactions in the cancer context to design inhibitors capable of eliminating tumors with a minimum of toxicity to normal cells.

In another study, published in the *American Journal of Physiology-Heart and Circulatory Physiology*, the researchers used an antibody to inhibit PDIA1 on the surface of vascular cells and observed the effects of stimulation with several different mechanical forces, such as stretching and alterations to the rigidity of the extracellular matrix.

Resulting from research conducted during Leonardo Yuji Tanaka's postdoctoral internship with support from FAPESP, the study concluded that surface PDIA1 inhibition affected the cytoskeleton, an intracellular framework of filaments, thereby hindering cell migration.

"PDIA1 is fundamental for the ability of cells to migrate within the organism, and so it mustn't be completely inhibited. When the surface portion, which corresponds to less than 2% of total PDIA1, is silenced, the cell survives but loses fine regulation of cell direction during migration. This can be leveraged in the search for new disease mechanisms and drugs," Laurindo explained.