Diabetes and Cancer: One Gene, Two Stories

By Arvin Gouw, M.A.

There have been many genetic and epidemiological studies linking metabolism and cancer[1-3]. The study highlighted here focuses on the link between type 2 diabetes and a gene that plays a major role in suppressing cancer. The gene is called phosphatase and tensin homologue, otherwise known as PTEN. Mutated, and thus dysfunctional, PTEN has been found in many types of cancer[4,5]. PTEN loss of function can cause what is known as the Cowden syndrome, a rare disease which predisposes one to cancer[6-9]. PTEN functions as a tumor suppressor, meaning this gene is lost or silenced as cancer progresses[10,11]. PTEN suppresses a signaling pathway that cancer cells need for survival, in particular one called the PI3K pathway[12]. The PI3K pathway is also important in the workings of insulin, the hormone that causes cells in the body to take up the simple sugar molecule glucose that is in the blood stream[13,14]. Insulin is also the very hormone that type 2 diabetes patients need, because of their insensitivity to insulin—diabetic patients don't take up glucose into their cells as well as other people. Since PTEN plays a major role in both how cancers grow and how they take up nutrients in the blood, Aparna Pal et al. from the Oxford Centre for Diabetes Endocrinology and Metabolism decided to study the relationship between PTEN and insulin sensitivity. They hypothesized that Cowden patients who have only one functional copy of PTEN out of the two, would have higher sensitivity to insulin, due to less suppression of the PI3K pathway by PTEN.

They measured insulin signaling of muscle and fat tissue samples from 5 Cowden patients and 5 normal, healthy adults by taking biopsies, or tiny pieces of tissue. They also looked at insulin sensitivity, the ability of the body to take glucose out of the blood stream, and pancreas function, the organ where insulin is produced, from 15 Cowden patients compared to 15 healthy adults. They then compared the body composition of 15 Cowden patients with 2,097 healthy adults to see if there was any correlation between PTEN loss of function and obesity.

Their results show that patients with lower PTEN function have lower insulin resistance, implying decreased risk for type 2 diabetes. As predicted, lower PTEN function leads to decreased inhibition of the PI3K pathway, which is a growth promoting pathway. This increased activity of the PI3K pathway was detected by the increased phosphorylation, or modification, of a downstream partner protein called AKT. Increased AKT phosphorylation indicates elevated PI3K activity, because AKT is a player in the classical way through which PI3K is understood to propagate its growth signal. Moreover, patients who carry a PTEN mutation were on average more obese than the general population, based on their body-mass index (BMI). BMI is the weight of a person in kilo-

grams divided by the square of that person's height in meters.

Thus, this study by Anna Gloyn and colleagues concludes that PTEN mutations are neither altogether bad nor altogether good. PTEN mutations correlate with increased risk for cancer and obesity on the one hand, but decrease the risk of type 2 diabetes.

Arvin Gouw, M.A., is Associate Editor of Biological Sciences at Cancer InCytes. He is also a Ph.D. candidate at Johns Hopkins University.

References

1. Q. Li, J. Zhang, Y. Zhou, L. Qiao, Obesity and gastric cancer. Frontiers in bioscience : a journal and virtual library 17, 2383 (2012).

2. R. Jacobs, P. Voorneveld, L. Kodach, J. Hardwick, Cholesterol metabolism and colorectal cancers. Current opinion in pharmacology, (Aug 8, 2012).

3. D. Corella, J. M. Ordovas, Interactions between dietary n-3 fatty acids and genetic variants and risk of disease. The British journal of nutrition 107 Suppl 2, S271 (Jun, 2012).

4. J. Zhang et al., PTEN maintains haematopoietic stem cells and acts in lineage choice and leukaemia prevention. Nature 441, 518 (May 25, 2006).

5. M. F. Berger et al., The genomic complexity of primary human prostate cancer. Nature 470, 214 (Feb 10, 2011).

6. M. H. Tan et al., Lifetime cancer risks in individuals with germline PTEN mutations. Clinical cancer research : an official journal of the American Association for Cancer Research 18, 400 (Jan 15, 2012).

7. R. Pilarski, J. A. Stephens, R. Noss, J. L. Fisher, T. W. Prior, Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. Journal of medical genetics 48, 505 (Aug, 2011).

8. F. Bourdeaut et al., Homozygous PTEN deletion in neuroblastoma arising in a child with Cowden syndrome. American journal of medical genetics. Part A 155A, 1763 (Jul, 2011).

9. R. Kersseboom et al., PTEN in colorectal cancer: a report on two Cowden syndrome patients. Clinical genetics 81, 555 (Jun, 2012).

10. S. Cedres et al., Exploratory analysis of activation of PTEN-PI3K pathway and downstream proteins in malignant pleural mesothelioma (MPM). Lung Cancer 77, 192 (Jul, 2012).

11. M. S. Song, L. Salmena, P. P. Pandolfi, The functions and regulation of the PTEN tumour suppressor. Nature reviews. Molecular cell biology 13, 283 (May, 2012).

12. S. Jia et al., Essential roles of PI(3)K-p110beta in cell growth, metabolism and tumorigenesis. Nature 454, 776 (Aug 7, 2008).

13. A. Pal et al., PTEN mutations as a cause of constitutive insulin sensitivity and obesity. The New England journal of medicine 367, 1002 (Sep 13, 2012).

14. G. Jiang, B. B. Zhang, Pi 3-kinase and its up- and downstream modulators as potential targets for the treatment of type II diabetes. Frontiers in bioscience : a journal and virtual library 7, d903 (Apr 1, 2002).