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Commentary

Is there an Association between ß-Cell Function and Cancer Risk?

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A review by Gristina et al. (Gristina et al., 2015) examined in detail the association between cancer and diabetes, confirming that type 2 diabetes (T2DM) and insulin resistant states are associated with an increased risk of several cancers. Similarly, a meta-analysis of 19 studies, both cross-sectional and prospective, showed a positive association between serum glucose and risk of cancer (Crawley et al., 2014). Obesity, particularly abdominal obesity, is a common risk factor for both cancer and T2DM, as are age, 'poor diet', physical inactivity, smoking and alcohol consumption thus these risk factors are potential confounders of associations between glucose and cancer risk. In contrast to the previous associations observed between impaired glucose regulation and cancer risk, the recent study by Falk et al. (Falk et al., 2017), in this edition of *EBioMedicine*, has shown that in healthy middle-aged men, low blood glucose concentrations in the first 10 min of an intravenous glucose tolerance test, but not fasting glucose or values later during the IVGTT, were associated with the development of cancer over the subsequent 40 years of follow-up. These men at increased risk of cancer had no evidence of impaired glucose regulation. The association was independent of age, fasting glucose, smoking, physical fitness, body weight and height, although no measures of diet or alcohol use were available.

Loss of the first phase insulin response is believed to be the first detectable defect in beta-cell function (MacDonald et al., 2005), thus men with optimal glucose regulation were at increased risk of cancer relative to those with less rapid glucose clearance. This is in contrast to most of the literature linking diabetes or abnormal glucose tolerance with increased cancer risk. What could be the mechanism for this? The authors of the current paper have noted the importance of glucose transporters, GLUT 1 and GLUT 2, and hexokinase which are responsible for glucose sensing and release of insulin from pre-docked insulin granules in the β-cells (MacDonald et al., 2005). In a healthy β-cell, glucose derived metabolites are directed to mitochondrial oxidative phosphorylation, which provides ATP, necessary for insulin exocytosis (MacDonald et al., 2005). This is achieved by glucose directly suppressing the pentose phosphate pathway in a dose-dependent manner (Schuit et al., 1997) and disallowance of monocarboxylic acid transporters and lactate dehydrogenase isoforms (Quintens et al., 2008), thus blocking alternate glucose metabolic pathways. If these usually suppressed pathways are active, resulting in slower glucose uptake and a change to predominantly anaerobic glycolysis, with pyruvate directed to lactate rather than ATP production, glucose sensing and insulin secretion will be compromised (Cantley et al., 2010).

Tumour cells take up a lot of glucose and it was observed by Warburg in the 1920s that they metabolised this utilising glycolysis, to produce ATP via lactate, rather than mitochondrial oxidative phosphorylation producing ATP (Shaw, 2006), thus contrasting with healthy β-cells.

Both β-cells and tumour cells appear to be regulated via activity of Hypoxia Inducible Factor (HIF), but in β-cells activation of this impairs function resulting in post-prandial hyperinsulinemia by switching glucose metabolism from oxidative to anaerobic glycolysis, akin to the Warburg effect described above (Cantley et al., 2010). Thus the current evidence suggests that β-cells with impaired function, which would be expected to result in higher 10 min glucose concentrations, could be more prone to development of cancer, in contrast to the current observations.

Another potential link between cancer and β-cell function is through micro-RNA, specifically miR-375 has been identified as a tumour suppressor and is downregulated in cancer (Yan et al., 2014), but also has an important role in β-cell function. A reduction in miR-375 promotes insulin secretion abolishing suppression of its target genes (Hashimoto & Tanaka, 2017), hence this might be an area worth studying in response to the findings of the current study.

At present researchers from cancer and diabetes fields are independently researching the aetiology of their respective diseases but the current epidemiological observations suggest there could be a link which needs to be further investigated.

Conflict of Interest

The author declares no conflict of interest.

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