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Opposing Effects of Antidiabetic Interventions on Malignant Growth and Metastasis

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Type 2 diabetes is associated with increased risk of malignancies, whereas antidiabetic interventions like physical exercise or metformin reduce cancer incidence. A recent publication shows that one diabetes treatment approach, namely incretin-related DPP4 inhibitors, increases metastatic capacity by activating the antioxidant transcription factor NRF2 to decrease reactive oxygen species (ROS) levels.

Type 2 diabetes mellitus (T2Dm) is a multifactorial metabolic disease that affected 422 million adults worldwide in 2014, and caused 1.5 million deaths in 2012 (www.who.int/diabetes/global-report/en/). Patients experience reduced healthspan due to complications including heart attack, stroke, kidney failure, leg amputation, vision loss, nerve damage, and increased incidence of some malignant disorders with strongest evidence for breast, colorectal, and endometrial cancer as well as cholangio-carcinoma. Besides physical exercise, multiple pharmacological treatment concepts for T2Dm and its complications are available, including alpha-lipoic acid (ALA), an antioxidant that may ameliorate diabetic neuropathy, and so-called incretins, namely GIP and GLP-1, to promote insulin secretion and/or sensitivity. GLP-1 is degraded and hence inactivated by an enzyme named dipeptidyl peptidase-4, and inhibitors of the latter (DPP4-Is), like saxagliptin (Sax) or sitagliptin (Sit), have hence become integral parts of modern treatment concepts of T2Dm. A recently published study suggests that Sax, Sit, and ALA accelerate tumor metastasis in experiments employing cell culture as well as xenograft mouse models (Wang et al., 2016).

The acceleration occurs through activation of NRF2, a transcription factor previously established to promote antioxidant and stress defense in multiple organisms including humans. Activity of NRF2 is controlled by an oxidation-sensitive cysteine residue of a co-factor KEAP1. When cysteine 151 of KEAP1 is in the reduced state, NRF2 undergoes proteasomal degradation. By contrast, oxidation of cysteine 151 dissociates KEAP1 from NRF2, the latter becoming transcriptionally active. While reactive oxygen species (ROS) have been previously shown to induce antioxidant defense through such dissociation of NRF2 from KEAP1, the authors here show that Sax, Sit, and possibly ALA may use the same mechanism. They show that all three compounds induce antioxidant defense by either acting as an antioxidant per se (ALA), or by inducing NRF2 (Sax, Sit) to indirectly induce expression of antioxidant enzymes. The latter occurs through impairment of KEAP-1-dependent ubiquitination of NRF2, and a concomitant reduction in ROS levels (Figure 1). By either mechanism, increased metastasis capacity was observed using migration and Matrigel assays, as well as in vivo experiments in mice. Conversely, inhibition of NRF2 attenuates metastatic capacity both in vitro and in vivo. Lastly, the authors associate increased metastasis with NRF2 expression in human liver cancer specimen to altogether conclude that specific antidiabetic drugs may promote metastasis in states of T2Dm through activation of antioxidant defense in an NRF2-dependent manner.

In addition to the above-mentioned incretins, many other peptides have been identified as DPP4 substrates, including eight different chemokines and neuropeptides, namely CXCL2, 6, 9, 11, and 12, as well as CCL11 and 22. Moreover, hormones like NPY and PYY are both cleaved by DPP4. Since NPY plays a role in the modulation of neuroimmune crosstalk by multiple mechanisms, this opens the possibility that carcinogenesis, tumor progression, or metastatic spread may be modified by DPP4-Is independent of incretin action.

These findings contribute to the mounting body of evidence that antioxidants reduce healthspan (Ristow, 2014), and may promote both cancer growth as well as metastatic potential, both of which have been recently demonstrated experimentally (Le Gal et al., 2015). Concurrently, epidemiological data from large intervention trials suggest that antioxidants may increase overall mortality, and specifically incidence of gastrointestinal and other cancers in humans (Bjelakovic et al., 2014).

Given the recent findings (Wang et al., 2016), should treatment of T2Dm or diabetic neuropathy be adjusted accordingly? There is insufficient evidence for ALA being effective in ameliorating neuropathy, mostly due to poor methodology of the few and small intervention trials available. Based on this, the authors' vote is tending to lean against the future use of ALA. By contrast, DDP4-Is, including Sax and Sit, have been clinically shown to be effective in improving key parameters of glycemic control in type 2 diabetics. Balancing the latter advantages versus a potentially increased metastasis risk seems scientifically difficult, and will mainly depend on future epidemiological observations from diabetics receiving

either one of these two drugs. Nevertheless, and as stated by the authors (Wang et al., 2016), use of the latter in diabetics with known malignant disease is definitely questionable. Moreover, it should be mentioned that other DDP4-Is, namely alogliptin, linagliptin, and vildagliptin, were also found to activate NRF2 (Wang et al., 2016), i.e., should not be considered preferred alternatives to the two DPP4-Is, Sax and Sit, studied in more detail in the current study. Rather, all DDP4-Is seem to activate NRF2, while activation of this transcription factor seems to counteract the tumor suppressor p53 (Faraonio et al., 2006) and reduces apoptosis and autophagy (Rao et al., 2010), all of which are known to limit propagation of malignant disorders.

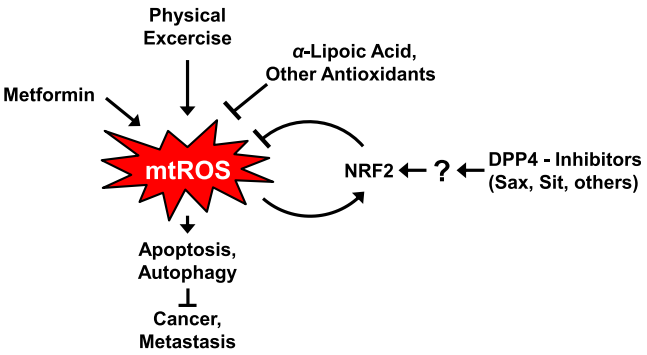

Figure 1. Mitochondrial ROS and Its Upstream Modifiers in the Control of Cancer and Metastasis

Antidiabetic interventions like physical exercise and metformin induce formation of mitochondrial reactive oxygen species (mtROS), while antioxidants like alpha-lipoic acid quench the formation of such free radicals. Likewise, and as elaborated on in the current study (Wang et al., 2016), antidiabetic DPP4-Is like Sax and Sit somehow activate the transcription factor NRF2, which in turn induces the endogenous antioxidant defense of the cell, culminating in increased metastatic capacity.

By contrast, other antidiabetic interventions are known to even reduce cancer incidence (and likely metastasis) in model systems and humans: (1) Physical exercise is considered a first-line treatment of T2Dm and, also independent of diabetes, is associated with decreased cancer incidence. Exercise activates hepatic AMP-dependent kinase (AMPK), increases glucose metabolism independent of insulin, and notably induces mitochondrial ROS production, which is required for improved glucose tolerance (Ristow et al., 2009). (2) The biguanide metformin, also an activator of AMPK as well as an inducer of mitochondrial ROS (Brunmair et al., 2004), is the only antidiabetic drug that not only improves glucose metabolism, but also extends the lifespan of diabetics, also by reducing the incidence of malignant disease. This prime proficiency as a so-called "exercise mimetic" has led to the initiation of a remarkable intervention trial in the healthy, i.e., particularly non-diabetic, elderly (Check Hayden, 2015).

Taken together, the data presented in this publication further extend previous evidence that ROS-lowering interventions contribute to growth and metastasis of malignant entities. More importantly, they raise the possibility that DPP4-Is may exert unexpected antioxidant action through NRF2 also in humans. If found to be accurate, this would bring the pre-existing debate on a potential link of DPP4-Is to specifically pancreatic cancer (Butler et al., 2013 and opposing response letters) to a new, more generalized, and mechanistically distinct level, while epidemiological confirmation for either is currently pending. Current evidence suggests no increased risk of pancreatic cancer in patients taking DPP4-Is, while other types of cancer have not been systematically investigated (Wang et al., 2016 and references cited within). However, the number of patient years and the years of exposure are too small to draw a final conclusion regarding risk of malignancies for this class of antidiabetic drugs.

CONFLICTS OF INTEREST

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