

Energy and metabolic alterations in predisposition to pheochromocytomas and paragangliomas: the so-called Warburg (and more) effect, 15 years on

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It happened in Pittsburgh, Pennsylvania, USA, in the year 2000. Bora Baysal, MD, PhD, a Turkish molecular biologist and trained pathologist, collaborated with physicians from Leiden, The Netherlands, who took care of the famous and etiologically puzzling Dutch paraganglioma family. He and his collaborators mapped the susceptibility gene locus to 11q23 and linked it to a gene encoding one of the four subunits of succinate dehydrogenase (mitochondrial complex II, SDHD), an enzyme that lies at the all-important crossroads of energy production, the Krebs tricarboxylic acid cycle and the glycolytic chain. The bombshell was dropped in the journal *Science* 15 years ago (Baysal *et al.* 2000). Paraganglioma syndrome ‘type 1’ (PGL1) finally had a genetic etiology: germline mutations of the SDHD gene. Within months, the SDH components B and C (together with SDHD umbrellaed under SDHx) were shown to predispose to similar tumors, if the respective genes (SDHB and SDHC) were mutated (Niemann & Müller 2000, Astuti *et al.* 2001). Soon there was evidence that not only head and neck paragangliomas but also pheochromocytomas and paragangliomas of the retroperitoneum and chest were caused by germline mutations of these genes (Gimm *et al.* 2000, Eng *et al.* 2003). These paradigm-shifting discoveries led to an onslaught, which continues today, of multiple studies both in paraganglioma and pheochromocytoma but more broadly into energy production and metabolism in carcinogenesis. Lest we be caught up in this marathon sprint, let us pause to loudly celebrate the 15th anniversary of this discovery. Let us linger for a moment to enjoy and acknowledge all

the achievements and progress in this field, highlighted by this special issue of *Endocrine-Related Cancer*. Baysal & Maher (2015), aptly, kick off this special issue with an overview of the genetics of the first two genes, SDHB and SDHD, in paraganglioma and pheochromocytoma.

SDHD became the first enzyme demonstrating that damage of the mitochondria is really a key feature in tumor cells opening a new chapter on the Warburg effect, the aerobic glycolysis by tumor cells. The paraganglionic tumors are, meanwhile, closely linked to mitochondrial insufficiency after the identification of structural abnormalities in three key enzymes, SDH, fumarate hydratase (FH) and malate dehydrogenase (MDH). Mannelli *et al.* (2015) present an erudite review on metabolism and pheochromocytoma/paraganglioma.

As appears typical of translational genetics, rapid scientific progress precedes clinical practice. For the latter, the neoplasia risk spectra had to be defined regarding age of manifestation, tumor location, tumor number, malignant tumors and tumor growth as well as longer-term outcome (Neumann *et al.* 2002, 2004, Gimenez-Roqueplo *et al.* 2003, Schiavi *et al.* 2005, Benn *et al.* 2006). In parallel, judicious effective clinical management had to be adjudicated, including adequate treatment for symptomatic and also for pre-symptomatically detected tumors. Organ sparing and endoscopic operation techniques were developed. With in-depth investigation and longitudinal follow-up, genetic counselors became equipped with risk estimates, incomplete penetrance (e.g., SDHB) and maternal imprinting (e.g., SDHD). With the diverse

locations of the paraganglial tumors and the subsequent identification of extra-paraganglial tumors such as epithelial thyroid cancers, renal cell carcinomas and, more recently, pituitary tumors (Lopez-Jimenez *et al.* 2008, Xekouki *et al.* 2012, Varsavsky *et al.* 2013, Denes *et al.* 2015), it became obvious that a multidisciplinary care (and research) strategy would optimally serve patients and families. As such, Benn *et al.* (2015) review the state-of-the-art knowledge on clinical manifestations of paraganglioma syndromes type 1–5. O'Toole *et al.* (2015) review the recent association of pituitary adenomas, and Tischler & deKrijger (2015), our reference pathologists, touch a problem that has been widely forgotten: the key role of the pathologist in the diagnosis and management of pheochromocytoma and paraganglioma and the identification of occult heritable cases.

When a major strategy of risk management is based on early diagnosis and surveillance, imaging technologies should continually improve and use energy and metabolic alterations in predisposition to pheochromocytomas and paragangliomas. Castinetti *et al.* (2015) redefine the position of nuclear medicine imaging of paraganglial tumors, especially those with still normal catecholamines/metanephrines or those with malignant spread detected by computerized tomography (CT) scanning and magnetic resonance imaging (MRI) from the viewpoint of the underlying germline mutations or a given malignant spread. New and old tracers had to be checked for their relevance for the diagnosis.

After the initial flurry of SDHx, it appeared that there remained many clinical high-risk individuals and families who were unaccounted for. It took a decade to characterize additional susceptibility genes, and again energy and metabolic alterations were shown to be affected: SDHA germline mutations for pheochromocytoma (Burnichon *et al.* 2009), SDHAF2 for familial head and neck paragangliomas (Bayley *et al.* 2010), FH (Castro-Vega *et al.* 2014), and most recently MDH2 in malignant pheochromocytoma (Cascón *et al.* 2015).

Exiting are cross-phenomenons of oxygen-sensing enzymes involved in the pathogenesis of extra-paraganglionic tumors. Structural alterations of the discussed key enzymes, in addition to the von Hippel Lindau (VHL) protein, by germline mutations followed by somatic mutation, e.g., biallelic inactivation, are involved in the pathogenesis of renal cancer. This was shown for the VHL gene (Neumann & Zbar 1997, Ebele *et al.* 2004), the SDHB gene (Vanharanta *et al.* 2004, Ricketts *et al.* 2008, Gill *et al.* 2011a,b), the SDHC gene (Malinoc *et al.* 2012) and the SDHD gene (Ricketts *et al.* 2012) in clear cell renal cancer

and is likely to occur also for the FH gene in papillary renal cell cancer type 2 (Tomlinson *et al.* 2002).

Finally, as is the case for many cancer predisposition genes, these uncommon paraganglioma and pheochromocytoma susceptibility genes and their metabolic pathways have been shown with time to play a major role in both sporadic paraganglial and extra-paraganglial neoplasias.

'If you want to find the secrets of the universe, think in terms of energy, frequency and vibration'

— Nikola Tesla

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