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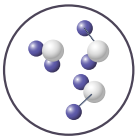

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Editorial

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Metabolism and Metabonomics in Cancer Risk Assessment, Diagnosis, Prognosis and Treatment

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Cancer is a genetic disease – changes to the cell's DNA lead to malignant transformation and known hallmarks of cancer. Genetic or epigenetic mutations leading to altered expression levels and activation of oncogenes and oncosuppressor genes reprogram metabolism as well and this further promotes tumor progression. There are now many experimental and clinical proofs of the significance of cancer metabolic phenotype in cancer's development, growth and metastasis [1,2]. Warburg's seminal finding, that tumor cells consume more glucose then equivalent normal cells [3,4], has been observed in a wide variety of cancers and is exploited clinically in ^{19}F-deoxyglucose positron emission tomography (FDG-PET). Altered glucose consumption and energy production is only one of many changes in metabolic processes required for cancer growth and survival. A majority of tumors have increased *de novo* fatty acid synthesis; increased choline consumption, often increased reliance on glutamine, reliance on several pseudo-essential amino acids; enhanced pentose phosphate pathway activity [5]. Many of these alterations to metabolism in cancers are exploited in methods such as MRI spectroscopy and also in the development of novel treatments [6]. At the same time, metabolites can also lead to cancer development. In some examples, mutation to an enzyme results in production of an altered metabolite or an increase in concentration of a standard metabolite and this can initiate cancer development. An example is a mutation to Isocitrate DeHydrogenase 1 and 2 (IDH1 and IDH2) that is observed in a subset of gliomas and leukaemias. Mutated versions of IDH1 and IDH2 catalyzes generation of 2-hydroxyglutarate (2HG) instead of α-ketoglutarate. 2HG has been indicated as an oncometabolite as it alters gene transcription through its effect on DNA and histone methylation and hypoxia inducible factor 1α (HIF1α) [7,8].

Metabolism in an organism also appears to have an influence on cancer development. Obesity has been indicated as one of the risk factors for development of some types of cancers [9]. Although a link between obesity and cancer is still mostly based on population studies, obesity leads to increased adipose tissue mass and this induces a number of metabolic changes in, for example, lipoprotein levels, cholesterol levels, increased secretion of leptin and inflammatory cytokines, all possible risk factors for cancer. Epidemiologic studies have also denoted Type 2 Diabetes as a risk factor for cancer development. Once again, clear molecular level, biological explanations of this relationship is still lacking [10].

Metabolomics and metabonomics, studying either a collection of metabolites present in a cell, tissue or organisms under specific conditions, or changes in these profiles in response to some stimulation can provide crucial information for untangling the puzzle of cancer metabolism and the relation between cancer and metabolic risk factors. Metabolic profiling of cells has already been used to determine specific characteristics of cancer metabolic phenotype, or cancer subtypes in a search for diagnostic and prognostic markers or drug targets [11]. Analyses of metabolic profiles in cancer tissues *ex vivo* and *in vivo* can indicate inhomogeneities in metabolism of cancerous and adjacent normal tissues [12,13]. Furthermore, metabolic markers in tissues can be used for diagnosis, prognosis and treatment planning or follow-up with several examples already in clinical use [14,15]. Direct analysis of body fluids, e.g. blood and urine, has also been extensively used to characterize possible risk factors or indicators of cancer. Although many of these examples are highly suspect [16], particularly as diagnostic tools (where confounding factors are a major issue), changes in blood metabolic profiles, for example, in cancer can indicate dependences of cancer cells and possibly lead to drug leads. As an example, arginine and asparagine are essential amino acids for cancer cells and, therefore, reduction in their plasma concentration has been proposed as a therapy [6].

Metabolomics and metabonomics are (re)-establishing their place as central "omics" methodologies. An increasing number of publications show their use independently or in combination with other "omics" methods as well as a source of crucial data for systems biology analysis. Studying metabolism and metabolites in an unbiased way can be expected to provide direct information needed to understand and take advantage of cancers' unique metabolism for both diagnosis and treatments.

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