Natural cancer therapy based on a ketogenic diet with master amino acid pattern and vitamin D-binding protein-based immunotherapy

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Given that cancer metabolism depends on glucose more than normal cell metabolism, the author established a natural cancer therapy: The SWISS Protocol based on a ketogenic diet with Master Amino Acid Pattern as well as a vitamin D-binding protein-based immunotherapy. In this article, the SWISS Protocol is outlined and the author also reports the case of a woman diagnosed with recurrent breast cancer who followed the Protocol for 3 weeks prior to her planned surgery. In this case, the nutritional strategy led to reversal of the neoplastic phenotype and suppression of oncogene expression HER2.

The author recently developed an integrated protocol – termed the ‘SWISS Protocol’ – for the natural immunotherapy of cancer that is based on three tenets: nutrition, immune surveillance and a healthy human microbiome (HM).

**Nutrition**

The first pillar ‘nutrition’ with a special type of ketogenic diet (KD) not only serves to better nourish the patient, this being important for his/her immune status as well as to prevent cachexia, but also directly targets the tumor metabolism, depriving it from sugar. In spite of the fact that some tumor types are able to metabolize under oxidative conditions, the majority of the tumors demonstrate a high glycolytic rate, especially the highly proliferating and aggressive ones (intracellular redosis, extracellular acidosis) [1]. With their concept of metabolic tumor typing (MTT), the author could show that 75% of the tumors either follow the pentose phosphate pathway (PPP) reinforced by glutaminolysis (Gln) or the PPP reinforced by glycolysis (Gly) [2,3]. This results in resistance to cytotoxic therapy and poor prognosis. The finding of a high glycolytic rate and aerobic Gly in tumours has been known since Otto Warburg (Warburg effect). The coincidence of high glycogen in the blood and the existence of tumor growth was also mentioned as early as 1885 in a paper published in Vienna from Ernst Freund, which was referenced in the New York Times in 1887, although it was fiercely rejected by his colleagues [4]). Between 1913 and 1915, others such as van Alstyne and Rous followed, presenting evidence of an accelerated tumor growth with a high carb diet [5].

Twenty-six years ago, it was again demonstrated that human carcinogenesis requires sustained Gly, and that diacylglycerol, a by-product of Gly, acts as a tumor promoter via activation of PKC, thus having an enormous capacity to make cancer cells resistant to all types of anticancer treatments [6]. At the same time, cancer cells have the ability to express fatty acid synthase (FAS), being able to produce large amounts of diacylglycerol through de novo synthesis from glucose and, therefore, are under constant pressure to divide. To summarize, Gly and PPP together more efficiently induce and sustain carcinogenesis than mutagenic chemicals [7–9].

In the SWISS Protocol, the author adopted an isocaloric KD based on a special amino acid formula, which does more than simply starving the tumor by depriving it from, for example, diacylglycerol. Due to the use of MAP, the author was able to supply high amino acid intake in cancer patients, even where...
the classical KD would be a suicide mission (e.g., pancreas, liver, kidney cancer). This is due to the fact that the MAP only produces minimal amounts of glucose and nitrogen waste (<1%), no enzymes are needed for its assimilation, and at the same time, it delivers the highest protein nutritional value (>99% net nitrogen utilization) worldwide [10]. This prevents cachexia and well-nourishes the patient with protein building blocks without overloading his/her liver and kidneys with nitrogen waste or sugar.

In addition to KD with MAP, Ruggiero and colleagues developed a functional food rich in glycosaminoglycans that are natural inhibitors of PKC without any side effects [11]. They discovered the effects of a probiotic preparation – for example, yogurt or kefir – containing vitamin D-binding protein macrophage-activating factors (DBP-MAF). Certain strains of microorganisms produce enzymes, which convert milk Gc-protein into active DBP-MAF. These products are known to modulate the immune response in mice, increasing the phagocytic activity of peritoneal and pulmonary macrophages [12]. It is also known that probiotic yogurt consumption is associated with an increase of CD4 count among people with HIV/AIDS [13].

Healthy HM
During the last decade, the HM with its symbiotic flora has been discovered as a ‘virtual’ organ crucial for the development of normal physiology in humans as well as of great importance for our immune system and even brain health. An intact blood–brain barrier (BBB) is crucial for the healthy development and functioning of our brain. The BBB with its tight junctions controls the passage and exchange of substances between the bloodstream and the brain, thus protection the brain from toxins. In a current study published in Science Translational Medicine, the international interdisciplinary research team at Sweden’s Karolinska Institute and colleagues in Singapore and the USA demonstrate that the transport of molecules across the BBB is influenced and modulated by gut microbes, which therefore play an important role in the protection of the brain. The BBB with its gatekeeper function also ensures homeostasis of the CNS. In the mentioned study, the authors reported that mice with a germ-free gut not only showed increased permeability compared with the pathogen-free mice with a normal gut flora but also developed inflammatory processes in the brain [15]. Additionally, the important role of the microbiome in cancer is testified by more than 1000 peer-reviewed articles published in the last few years on this topic. The reconstitution of the healthy core HM is equivalent to the reconstitution of the entire immune system and, therefore, to a generalized rebalancing of the immune system. In other words, targeting the gut flora is not an unspecific ‘stimulation,’ but rather a ‘transplant’ of the immune system. This is due to the peptides and proteins formed during the fermentation process as well as to the biologically active proteoglycans that are naturally present, achieved through the development of an all-natural, functional food. It contains more than 40 microbial strains that reconstitute the healthy human core microbiome as well as peptides and proteins formed during the proprietary fermentation process that have immunostimulant, antiaging, anticancer, neuroprotective properties as shown in the study mentioned. Natural glycosaminoglycans inhibit PKC and, hence, tumorigenesis.

Case report: mammary adenocarcinoma
Here, the author reports the case of a woman diagnosed with recurrent breast cancer who followed the SWISS Protocol for 3 weeks prior to...
planned surgery without any other treatment. The nutritional strategy led to unexpected changes in tumor markers within a short time.

**Background & diagnosis**

The woman was diagnosed with mammary adenocarcinoma in the right breast in 1985 at the age of 37. The diagnosis was followed by partial resection (quadrantectomy) with lymphadenectomy and postsurgical irradiation. In 1999, at the age of 51, an adenocarcinoma was diagnosed in the left breast. The diagnosis was followed by amplex resection irradiation and antienestrogen receptor treatment for 6 years as a preventive measure. In March 2014, at the age of 66, an infiltrating adenocarcinoma was diagnosed in the remaining part of the right breast that had been operated and irradiated in 1985. In the proximity of the areola, in the superior external quadrant, an inhomogeneous lesion of 14 × 9.2 × 12 mm³ with irregular margins was detected by ultrasonography. Immediately after this diagnosis, the patient underwent ultrasound-guided fine-needle biopsy, and four specimens from different areas of the lesion were examined. MRI was performed to assess local extension of the tumor. The hospital’s diagnosis stated infiltrating mammary adenocarcinoma, malignant neoplastic lesion. Consistent with the aggressive nature of the cancer in this patient, preoperative biopsy showed estrogen receptor (ER) (clone SP1) positive 90%, intensity of staining ‘marked’ and progesterone receptor (PgR) (clone 1E2) positive <1%, intensity of staining ‘weak’. The cellular marker for proliferation Ki-67 (clone MIB1) was increased by 30%. The aggressive nature of this cancer was consistent with significant positivity for the oncogene c-erbB-2 (HER2) (polyclonal A 0485), with >10% of positivity and a score of 2+ as well as with the report of the MRI, describing an area of impregnation of about 6 mm in correspondence of the pectoralis muscle that led to the suspicion of infiltration of the muscle itself.

**Establishing the SWISS Protocol 3 weeks prior to operation**

The author established a strict KD regime based on MAP, the daily consumption of the functional food (yogurt) as described above, and frequent subcutaneous injections of multimolecular complexes (GcMAF) of vitamin D, oleic acid and vitamin D-binding protein. After 3 weeks of using the SWISS Protocol, the patient underwent mastectomy. During the operation, samples of the pectoralis muscle were taken to assess the infiltration documented in the preoperative MRI. Histological analyses were performed on the surgical specimens. The results as shown in the hospital report were impressive and describe c-erbB-2/HER2 expression negative, increase in the PgR expression (i.e., 20 vs <1%) and no invasion of the blood or lymphatic vessels around the tumor was observed. Furthermore, surprisingly, no neoplastic proliferation in the pectoralis muscle was observed. The status of the ER and Ki-67 markers was unaltered.

**Discussion**

A very recent study demonstrates that vitamin D supplementation in patients with nonmetastatic HER2-positive breast cancer was associated with improved disease-free survival, and this effect was attributed to the interplay between the VDR signaling and the HER2 signaling through the ErbB2/AKT/ERK pathway. These results are consistent with the observation that oral administration of a vitamin D analogue prevents mammary tumorigenesis driven by HER2 overexpression. On the other hand, it has been demonstrated that oleic acid down-regulates HER2 expression in cancer cell lines. Additionally, these effects of oleic acid are well assessed and led the author to a ‘wonder’ article by 17th century writer Giacomo Castelvetro [16]:

'The Sacred Law of Salads' (i.e., “raw vegetables…plenty of generous [olive] oil”) – originally proposed in 1614 by Giacomo Castelvetro in his book, *The Fruit, Herbs & Vegetables of Italy*, might be considered the first (unintended) example of customized diets for breast cancer prevention based on individual genetic makeup (i.e., nutraceuticals against human breast carcinomas bearing HER2 oncogene amplification/overexpression). First, the so-called salad vegetables dietary pattern (i.e., a high consumption of raw vegetables and olive oil) appears to exert a protective effect mostly confined to the HER2-positive breast cancer subtype, with no significant influence on the occurrence of HER2-negative breast cancers. Second, all the main olive oil constituents (i.e., the -9 monounsaturated fatty acid oleic acid and polyphenolic compounds such as the secoiridoidoleuropein or the lignan 1-[-+] -acetoxypinoresinol) dramatically reduce HER2 expression and specifically induce

“The reconstitution of the healthy core human microbiome is equivalent to the reconstitution of the entire immune system...”
apoptotic cell death in cultured HER2-positive breast cancer cells, with marginal effects against HER2-negative cells. Third, an olive oil-rich diet negatively influences experimental mammary tumorigenesis in rats likewise decreasing HER2 expression levels.

An association between the KD based on MAP and the consumption of probiotic MAF-yogurt as well as MAF-Oleic-Acid/D3 injections undergone by the patient and the changes on HER2 expression may be hypothesized on the basis of downregulation of HER2 expression via the diacylglycerol-PKC pathway. More recently, it has been demonstrated that PKC is responsible for the preferential recycling of the HER2 protein in breast cancer cells and it has been hypothesized that this PKC-dependent endosomal signaling may be responsible for the oncogenic potential of HER2. Therefore, a nutrition-based decrease of glucose available for de novo synthesis of diacylglycerol and a reduced PKC activation may explain the negativity of HER2 expression observed in this patient. Thus, because of reduced PKC activation, most of the HER2 protein would be driven by endocytic traffic into lysosomes instead of recycling, and thus limiting the overexpression of HER2.

Conclusion & future perspective
The author developed an immunotherapeutic protocol based on natural nutrition (KD based on MAP) together with probiotics and nonprotein vitamin D, oleic acid, proteoglycan-MAF activation that reconstitutes the healthy HM and provides a number of natural molecules endowed with immunomodulatory and anticancer activities, preventing at the same time cachexia. The nonprotein complexes will substitute the current GcMAF approach based on vitamin D-binding protein associated with oleic acid and vitamin D. So, former GcMAF will be replaced through a much more efficient nonprotein GcMAF-analogue. These novel nonprotein complexes (GcMAF-analogue) have the advantage of improved pharmacodynamics, improved safety, improved stability, improved versatility and they have the potential of revolutionizing the field of immunotherapy.

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**Commentary**

