Natural medicine: a ‘new frontier’ in oncology?

Frequently, someone claims about the possibility to fight cancer with natural remedies, generally eliciting skepticism in a large proportion of scientists, doctors and general public. However, the possibility to investigate *vis sanatrix naturae*, i.e. the capability of nature to heal and cure, by modern technologies furnishes a rational support to old observations, regarding the possibilities that a particular life style or the use of natural substances contained in the food could positively influence our well being.

Epidemiological studies indicate that the Mediterranean diet may protect against several kinds of cancer in humans [1], even if case-control, cohort, and recent prospective epidemiological studies generated conflicting results, at least in breast cancer [2]. However, the ‘dietary fat hypothesis’ has been supported by a number of epidemiological, experimental, and mechanistic data, altogether providing evidence that dietary or exogenously derived fatty acids may play an important role in the promotion, evolution and/or progression of breast cancer [3].

Despite increasing interest in the evaluation of the life style and diet influences on cancer risk, the presence of a great number of individual variables can explain the difficulties in a clear definition of the putative role of each natural substance in the cancer prevention. The heavy consumption of cheese, butter, creamy sauces and other fat-containing foods by the French population could determine a greater incidence of certain types of cancer with respect to Americans; on the contrary, the incidence is lower in the French population and this has been attributed to a higher consumption of red wine [4, 5].

However, is the higher red wine use a causal intervention or a co-variant event? The answer to this question is very difficult.

The results of the study with the oleic acid (OA; 18:1n-9), largely present in olive oil, published in this issue of Annals of Oncology by J. A. Menendez et al. [6] is of particular interest not only for the presented results, but also for the methodological approach in such a complex and difficult field.

Although some conflicting epidemiological and experimental results on the role of mono-unsaturated fatty acids in breast cancer prevention may be partially explained, certainly there is relatively little understanding of the specific molecular mechanisms by which fatty acids such as OA may exert its effects on breast cancer.

Neoplastic development is a multi-step process, primarily induced by carcinogens, that begins with cellular transformation, progresses to hyperproliferation and culminates in the acquisition of invasive potential, angiogenic properties and establishment of a metastatic phenotype. Alterations in the expression of several genes during this process are well established.

The risk of acquiring specific types of cancer can be reduced by a regular consumption of certain fruits and vegetables that contain key elements, named phytochemicals, which interact in different phases of tumor progression [7]. Phytochemicals, such as genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, curcumin, 6-gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, and oleic acid, are contained in food like garlic, ginger, soy, curcumin, onion, tomatoes, cruciferous vegetables, chillies, green tea, red wine and olive oil and may have untapped therapeutic value [7]. It has been shown that these agents are largely present in the diet of populations with a low risk of acquiring solid tumors. From a molecular point of view, the accurate recent review of T. Dorai and B. Aggarwal [7] largely documents the phytochemical capacity to suppress cancer cell proliferation, inhibit growth factor signaling pathways, induce apoptosis, inhibit NF-kB, AP-1, and JAK-STAT activation pathways, modify multi-drug resistance, inhibit angiogenesis, suppress the expression of anti-apoptotic proteins, and inhibit cyclooxygenase-2. Moreover, these agents have been found to reverse chemoresistance and radioresistance [8–11].

The Menendez et al. paper [6] clearly demonstrates that OA can repress Her-2/neu oncogene overexpression and could represent a novel pathway through which individual dietary fatty acids may modulate both the etiology and the aggressive behavior of breast cancer disease. Moreover, exogenous supplementation with OA dramatically down-regulates Her-2/neu-coded p185Her-2/neu oncoprotein in human breast cancer cell lines, bearing amplification of the Her-2/neu oncogene. Importantly, OA-induced suppression of Her-2/neu overexpression was not significantly prevented by the effective scavenger of reactive oxygen species vitamin E, thus ruling out that lipid peroxidation may be involved in this effect. Finally, the results obtained suggest that dietary interventions based on OA may be even more beneficial when given in combination with novel therapies directed against Her-2/neu.

According to the authors, although caution must be applied when extrapolating *in vitro* results into clinical practice, this previously unrecognized property of OA in modifying Her-2/neu activity will contribute to understanding the molecular mechanisms by which individual fatty acids may regulate the malignant behavior of breast cancer cells and therefore be helpful in the design of future epidemiological
studies and, eventually, dietary counseling in breast cancer patients.

Paolo Marchetti
Medical Oncology,
University of L’Aquila, Italy

References