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Commentary

Tumor Liberated Protein (TLP) as Potential Target for Immunotherapy Associated to Nutraceutical Supplements

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The concept that the immune system can recognize and control tumor growth can be traced back to 1893 when William Coley used live bacteria as an immune stimulant to treat cancer, but the enthusiasm for cancer immunotherapy has been moderate due to limited clinical efficacy. This limited efficacy is due to the ability of tumor cells to avoid recognition and elimination by the immune system, allowing them to become established in the host (1). Over the past few decades, tremendous progress has been made in the understanding of how cancer evades the immune system, which in turn offers new ways to stop cancer immune evasion in favor of eliminating cancer cells.

TLP complexes (proteins released from tumors) show antigenic activity that may be applied for diagnostic aims and represent a target for immunotherapy. TLP antigens are proteins found in many cells, and one of the main components was first isolated from lung cancer tissues [1]. From this protein, it was obtained an epitope on whose basis it was possible to develope a rabbit anti-TLP serum [2]. In fact, the antibodies devolped against these antigens are able to mark lung carcinoma tissues and to recognize the specific sequences previously found in TLP [1]. In addition, TLP was found in sera from patients with lung and colorectal cancer, in lung and colorectal cancer tissues and cell lines [2] and detected in DHD-K12 cell line in vitro and in vivo, in metastases induced by DHD-K12 cell injection in rats [3]. Furthermore, TLP exerts specific mitogenic activity as its intradermic inoculation results in lymphocyte blastogenesis [4].

TLP can be detected in human sera using an ELISA assay. It is worthy of note the possibility to apply a kit able to measure sera TLP values as diagnostic tool for lung cancer. Infact, the identification of TLP in sera from healthy subjects may result in an early diagnosis, thus providing the possibility to exert preventive strategies including, among others, the intervention through the modification of life styles, and the consumption of nutraceutical supplements that may contrast the molecular mechanisms underlying the onset and the progression of lung cancer.

- vaccine
- life style

These 2 ways are not in contrast between them, but they should be done together. Infact, there is a plethora of phytocomplexes able to produce molecular mechanisms. Camellia sinensis consumption seems to exert preventive role on carcinogenesis. These activities are, atleast in part, due to the severals effects of (−) epigallocatechin gallate (EGCG). The mechanisms underlying the chemopreventive effects concern the affetcion of carcinogen-metabolizing enzymes, of cell-signaling pathways apoptosis induction, arrest of cell-cycle, transcription factors activation inhibition.

EGCG (1–40 μM) reduces human lung cancer cells proliferation upregulating p53 expression, resulting from the augment of p53 phosphorylation at Ser15 and Ser20 and the induction of its transcriptional activity [5]. Another protein involved in EGCG chemiopreventive activity is HIFα [6].

Furthermore, EGCG shows cytotoxicity against drug-sensitive and drug-resistant SCLC cells In both cell lines, DNA fragmentation and S-phase cell-cycle arrest were observed [7]. In particular this flavonoid was shown to inhibit cell proliferation in in erlotinib-sensitive and resistant cell lines, in addition to producing the same effect in H460 xenografts [8].

Green tea, EGCG and GTP exert preventive and therapeutic activities towards lung cancer in animals. Infact the oral administration of EGCG to nude mice augmented H1299 cells apoptosis through several mechanisms including the induction of oxidative DNA damage [9]. Theaflavin and EGCG inhibit proliferation at different stages of experimental lung carcinogenesis in the mouse model of benzo(a)pyrene [B(a)P]-induced lung carcinogenesis [10]. Furthermore, the administration of GTP and black tea polyphenols to Swiss albino mice decreased the

incidence of lungs diethylnitrosoamineinduced alveologenic tumors, as result of Akt expression, cox and nuclear factor kappa-B (NF-κB) inhibition [11].

Pomegranate (Punica granatum L., Punicaceae), is an edible fruit whose juices and extracts are rich in hydrolizable tannins such as punicalagin and punicalin. A pomegranate fruit extract (PFE) reduced cell-viability of human lung cancer A549 cells without affecting normal human bronchial epithelial cells. In particular, this vegetal extract, in A549 cells, produced cells arrest in G0–G1 phase and reduced the expressions of cyclins, cyclin-dependent kinases. The molecular mechanisms underlying this activity include the inhibition of MAPK, PI3K, phosphorylation of Akt, NF-κB and markers of cell-proliferation [12].

In the same work, it has been observed that PFE oral administration to nude mice with implanted with human lung cancer A549 cells resulted in a reduction of tumor growth, and delayed solid tumors formation. Also in the experimental models of lung cancer induced by B(a)P and N-nitroso-tris-chloroethylurea (NTCU), PFE oral administration inhibited cancer growth and progression, and angiogenesis, through several mechanisms including NF-κB, MAPK, PI3K, Akt phosphorylation inhibition [13].

Other plants extract able to inhibit cancer cells proliferation are those obrained by Urtica dioica L., [14] Artemisia annua, [15] among others. In addition, for several plants, such as Hedyotis diffusa Willd., the direct anticancer effect occuring through several mechanisms in associated to the ability to activate immunity [16]. Also several flavonoids, such as, vitexin, nobiletin were shown to inhibit lung cancer cells proliferation affecting a plethora of molecolar networks [17, 18]. The same observation may be exerted for many other classes on natural compounds such as stilbens including resveratrol and piceatannol, ellagitannins such as geraniin, Sanguiin H6, Oenothein B, phytosterols such as beta sitosterol, daucosterol whitaferin A [20-25].

In conclusion, the investigation of the anticancer activities of several plants extracts has provided some evidence for the potential clinical application. Many vegetal extracts and natural compounds act as anticancer agents exerting a cytotoxic effect against some cancer cells and increasing host immunity, potentialy increasing organism ability to fight cancer [26].

Conflict of Interest Statement

The authors declares no conflict of interest

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