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Review

Assessing the anticancer effects associated with food products and/or nutraceuticals using *in vitro* and *in vivo* preclinical development-related pharmacological tests

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ABSTRACT

This review is part of a special issue entitled "*Role of dietary pattern, foods, nutrients and nutraceuticals in supporting cancer prevention and treatment*" and describes a pharmacological strategy to determine the potential contribution of food-related components as anticancer agents against established cancer. Therefore, this review does not relate to chemoprevention, which is analysed in several other reviews in the current special issue, but rather focuses on the following: i) the biological events that currently represent barriers against the treatment of certain types of cancers, primarily metastatic cancers; ii) the *in vitro* and *in vivo* pharmacological pre-clinical tests that can be used to analyse the potential anticancer effects of food-related components; and iii) several examples of food-related components with anticancer effects. This review does not represent a catalogue-based listing of food-related components with more or less anticancer activity. By contrast, this review proposes an original pharmacological strategy that researchers can use to analyse the potential anticancer activity of any food-related component—e.g., by considering the crucial characteristics of cancer biological aggressiveness. This review also highlights that cancer patients undergoing chemotherapy should restrict the use of "food complements" without supervision by a medical nutritionist. By contrast, an equilibrated diet that includes the food-related components listed herein would be beneficial for cancer patients who are not undergoing chemotherapy.

1. Cancer

1.1. Introduction

Cancer imposes an enormous burden on societies in more and less economically developed countries alike. The occurrence of cancer is increasing due to the growth and ageing of the population, as well as the increasing prevalence of established risk factors, such as smoking, being overweight (relating to abnormal and/or inappropriate food consumption), physical inactivity, and changing reproductive patterns associated with urbanization and economic development [1]. Torre et al. [1] recently reviewed the cancer incidence worldwide, while Jemal et al. [2] performed this analysis for US cancer patients [2].

For Hanahan and Weinberg [3], the multistep development of human tumours includes sustained proliferative signalling, evasion from growth suppressors, resistance to cell death, the capacity of replicative immortality, induction of angiogenesis, activation of invasion and metastasis, the reprogramming of energy metabolism and evasion from immune destruction. These authors further report that cancers exhibit another dimension of complexity because they contain a repertoire of recruited, ostensibly normal cells that contribute to the "tumour microenvironment" [3]. Thus, cancerous tissue is highly heterogeneous, and this heterogeneity contributes to the ineffectiveness of current chemotherapy agents. The current review highlights that several food-related components can hinder the biological development of cancer as described by Hanahan and Weinberg [3].

1.2. Chemoresistance

1.2.1. Generalities

Modern chemotherapy is mainly based on the use of cytotoxic or targeted agents [4], usually applied after surgery and after or along

Abbreviations: CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; MDR, multidrug resistance; MTT, 3-(4,5-dimethylthazol-2-yl)-2,5-diphenyltetrazolium bromide; NCI, US National Cancer Institute

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with radiotherapy, to which immunotherapy can also be added. Most cytotoxic anticancer agents are of natural origin, while targeted therapies generally result from computer modelling followed by synthesis. However, both types of therapy, unfortunately, display major limitations with respect to cancer cell heterogeneity [4]. The major limiting factor for the use of cytotoxic drugs is their toxicity towards many healthy organs. However, targeted agents exhibit the same frequency and severity of toxicities as traditional cytotoxic agents, with the main difference being the nature of the toxic effects—e.g., alopecia, myelosuppression, mucositis, nausea, and vomiting for cytotoxic therapies versus vascular, dermatologic, endocrine, coagulation, immunologic, ocular, and pulmonary toxicities for targeted therapies [4]. Immunotherapy is also associated with limiting toxic effects [5,6].

Barber and colleagues [7] accordingly reported that understanding subclonal heterogeneity architectures and cancer evolution processes is critical for the development of effective therapeutic approaches, which can control or thwart cancer evolutionary plasticity. Arnedos et al. [8] stated that, although several successfully targeted agents have been developed in recent years, most tumours eventually develop drug resistance, potentially due to intratumoural heterogeneity and the selection of additional biochemical events. Ramos and Bentires-Alj [9] explained that the plasticity of tumour cells leads to the development of drug resistance by distinct mechanisms, including the following: (i) mutations in the target, (ii) reactivation of the targeted pathway, (iii) hyperactivation of alternative pathways, and (iv) cross-talk with the microenvironment. Dorel et al. [10] stated that signalling pathways implicated in cancer create a complex network with numerous regulatory loops and redundant pathways and that this complexity also explains the frequent failure of the one-drug-one-target paradigm of treatment, resulting in drug resistance in patients. These authors proposed that cancer treatment should be extended to a combination of therapeutic approaches to overcome the robustness of the cell signalling network [10]. As highlighted in the following section, the consumption of certain types of food components/diet regimens can help as an added weapon to combat certain types of cancer, in addition to conventional treatments. Indeed, many food-related components display distinct mechanisms of action in terms of anticancer effects. Thus, a diversified and equilibrated diet can be deleterious to several subpopulations within a given cancer as detailed in the following sections. However, it must also be emphasized that certain diet components can be deleterious for cancer patients with certain ongoing types of chemotherapy (as summarized at the end of the current review).

In addition to the mechanisms described above, cancer cellular drug resistance can also be associated with the altered expression of the ATP-binding cassette (ABC) family of transporters, the most common cause of multidrug resistance (MDR), alterations of DNA repair pathways, and resistance to pro-apoptotic stimuli [11]. Finally, the ineffectiveness of cancer chemotherapy is associated with the tumour microenvironment, hypoxia and the development of metastases, as detailed in the following sections. An anticancer agent that impairs the biology of the tumour microenvironment represents a promising and very innovative anticancer drug. This is the case, for example, for the tunicate metabolites trabectedin (marketed as Yondelis) and plitidepsin (in phase III clinical trials) [12].

1.2.2. Resistance to pro-apoptotic stimuli

The link between the evasion of apoptosis and cancer development is implicitly clear if one considers how many cells are produced each day and, hence, how many cells must die to make room for the new ones. Cells frequently experience noxious stimuli that can cause lesions in their DNA. These lesions need to be repaired efficiently, or, in the case of irreparable damage, the cell must be killed to prevent the subsequent division of aberrant cells that may fuel tumourigenesis. As reported by Kelly and Strasser [13], the detection of genetic lesions in human cancers that activate pro-survival genes or disable pro-apoptotic genes serves as direct evidence that defects in apoptosis can cause cancer. Evasion of apoptosis is thus a requirement for both neoplastic transformation and the sustained growth of cancer cells [13,14]. Mohammad et al. [14] remind us that most anticancer therapies trigger apoptosis and related cell death networks to eliminate malignant cells. However, deregulated apoptotic signalling, particularly the activation of anti-apoptotic systems, allows cancer cells to escape this programme, leading to tumour survival, therapeutic resistance and cancer recurrence. In other words, a promising anticancer drug should be a compound that kills cancer cells through the activation of non-apoptosis-related cell death pathways [15]. Mohammad et al. [14] recently reviewed the key apoptosis-resistance targets that include the following: (i) B-cell lymphoma 2 (Bcl-2) and myeloid cell leukaemia 1 (Mcl-1) proteins, (ii) autophagy processes; (iii) necrosis and necroptosis, (iv) heat shock protein signalling, (v) the proteasome pathway; (vi) epigenetic mechanisms, and (vii) aberrant nuclear export signalling.

Most, if not all, cancers associated with dismal prognoses resist pro-apoptotic insults. Examples include melanoma [16], glioblastoma (GBM) [17], and pancreatic [18], oesophageal [19], head and neck [20] and lung [21] cancers. Cancer metastases also fall into this category [22,23], and, as a result, approximately 90% of cancer patients die from tumour metastases [23–25].

1.2.3. Cancer stem cells

Similar to normal tissue, many tumours have a hierarchical organization where tumourigenic cancer stem cells (CSCs) differentiate into non-tumourigenic progenies [26,27]. Stem cells are often localized to hypoxic niches within tissues, and hypoxia-inducible factors (HIFs) play key roles in the maintenance of pluripotent and multipotent stem cells, as well as CSCs, which are also known as tumour-initiating cells [27]. Islam et al. [28] and Adorno-Cruz et al. [29] reviewed the roles of CSCs in the metastatic process, treatment resistance, and cancer recurrence via the activation of different signalling pathways, such as Notch, Wnt/β-catenin, transforming growth factor-β (TGF-β), Hedgehog, PI3 K/Akt/mTOR and JAK/STAT. Cojoc et al. [26] accordingly reported that strategies based on the combination of conventional therapies targeting bulk tumour cells and CSC-specific pathways bear significant promise to improve cancer treatment outcomes compared with monotherapies. Marucci et al. [30] recently reviewed the ability of 49 different natural products to influence CSC biology.

1.2.4. Hypoxia

The tumour microenvironment exerts a complex and strong influence on the tumour cell phenotype [31]. Hypoxia represents one of these tumour microenvironmental effects on cancer cell biology, and it occurs, for example, with poor tumour neoangiogenesis and increased oxygen consumption [31,32]. As also emphasized by Span and Bussink [31], hypoxia is a multifactorial phenomenon involving oxygen tensions ranging from < 0.01% (anoxia) to 5% and can be chronic, acute, or cycling, all with differential effects on tumour cells. When cancer cells face hypoxic conditions, they activate intracellular signalling pathways, including HIF-1-mediated gene expression, the unfolded protein response, and AKT-mammalian target of rapamycin signalling [31]. Activation of these pathways, in turn, induces aggressive, metastatic and treatment-insensitive tumours [31–35]. Unwith et al. [36] accordingly reported that HIF-1 overexpression in many aggressive cancer types, as well as its role in the establishment of metastatic disease and treatment resistance, makes it an attractive potential target for cancer drug development. Irregular blood flow and large distances between functional blood vessels lead to poor drug distribution within solid tumours [37]. Cells that are distal from functional blood vessels are not exposed to effective concentrations of the drug, resulting in therapeutic resistance.

1.3. The metastatic journey and cancer cell dormancy

Cancer-related mortality primarily results from the failure to cure