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Review

Understanding genistein in cancer: The "good" and the "bad" effects: A review

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ABSTRACT

Nowadays, diet and specific dietary supplements are seen as potential adjuvants to prevent different chronic diseases, including cancer, or to ameliorate pharmacological therapies. Soybean is one of the most important food components in Asian diet. A plethora of evidence supports the *in vitro* and *in vivo* anticancer effects of genistein, a soybean isoflavone. Major tumors affected by genistein here reviewed are breast, prostate, colon, liver, ovarian, bladder, gastric, brain cancers, neuroblastoma and chronic lymphocytic leukemia. However, it is not always clear if and when genistein is beneficial against tumors (the "good" effects), or the opposite, when the same molecule exerts adverse effects (the "bad" effects), favouring cancer cell proliferation. This review will critically evaluate this concept in the light of the different molecular mechanisms of genistein which occur when the molecule is administered at low doses (chemopreventive effects), or at high doses (pharmacological effects).

Contents

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1. Introduction

"Cancer is a pleiotropic disease." This definition, by Nancy R. Gough, is reported in a recent editorial (Gough, 2014) and encompasses very well the complexity of the term "cancer" which is not only caused by the abnormal growth of cells with the potentiality to invade different organs, but also by an impaired differentiation. A classical example is acute promyelocytic leukemia, APL, or a block in cell death programme (chronic lympocytic leukemia). A second level of complexity regards the ability of cancer cells to change over time. DNA massive parallel sequencing of tumors now enables the rapid identification of a myriad of genetic mutations that alter signaling pathways, affecting drug efficacy or resistance. This explains why drug resistance represents a common and undesirable event, occurring randomly in patients affected by the same tumor and in the presence of "molecular targeted" drugs. For these reasons, cancer still remains an incurable disease.

The World Health Organization (WHO) reports that every year there are approximately 38 million new cases of non-communicable diseases (NCD) with cancer representing the second cause of NCD with 8.2 million deaths, corresponding to 22% of all NCD in 2012 (World Health Organization, 2015a). It has been well recognized that 90–95% of cancers are caused by epigenetic factors, while the remaining are related to genetic factors (Anand et al., 2008; Esteller, 2008; Taby & Issa, 2010). Among the epigenetic factors, the WHO reports that one third of cancer deaths are caused by the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol use (World Health Organization, 2015a). Moreover, infections, radiation, and environmental pollutants are known as other common causes of cancers (Ames, Gold, & Willett, 1995; Boffetta, 2006). Currently, there is a strong urgency to find new therapeutic strategies for the treatment of cancers, especially for those that show drug-resistance, high risk of relapse, unavailability and/or poor therapeutic strategies. For this reason, much attention is paid to the therapeutic use of natural products, due to their high efficacy and low adverse effects (Cragg, Kingston, & Newman, 2011; Cragg & Newman, 2013; Demain & Vaishnav, 2011; Mehta, Murillo, Naithani, & Peng, 2010; Newman & Cragg, 2012).

Since ancient times, medicinal plants have been used for the treatment of different diseases due to their content of bioactive compounds (Balunas & Kinghorn, 2005; Nabavi, Daglia, Moghaddam, Habtemariam, & Nabavi, 2014; Nabavi, Nabavi, Mirzaei, & Moghaddam, 2012; Nabavi et al., 2013). It has also been reported that over than 60% of common anticancer drugs originate in nature (Cragg & Newman, 2005). In addition, the National Cancer Institute (NCI) in the USA examined the anticancer effects of different plant extracts, as well as other natural products (Snader & McCloud, 1994). Among them, flavonoids, widely found in different parts of plants, are known as the most important group of natural anticancer compounds (Bilotto et al., 2013; Clere, Faure, Carmen Martinez, & Andriantsitohaina, 2011; Genoux, Nicolle, & Boumendjel, 2011). The main chemical signature of flavonoids is the 15-carbon skeleton which contains two phenyl rings as well as one heterocyclic ring (Nabavi, Nabavi, Eslami, & Moghaddam, 2012; Nabavi, Nabavi, Mirzaei, et al., 2012).

Genistein, daidzein and glycitein (Fig. 1) are the most common and well known isoflavones in nature (Song, Barua, Buseman, & Murphy, 1998; Wang & Murphy, 1994). They contain a 3-phenylchromen-4-one skeleton without hydroxyl group substitution on position 2 (Coward, Barnes, Setchell, & Barnes, 1993). Genistein, present in soy foods at concentrations ranging from 1.9 to 229 mg/g, is reported to be the major anticancer constituent of soybean (Fukutake et al., 1996; Spagnuolo et al., 2015).

Although the literature of the past decade reports several excellent reviews on the biological activities of genistein, many of them are focussed on pathological conditions different than cancer and, even in the latter case, generally, the effects of genistein on a specific type of cancer have been reviewed. Therefore, the aim of the present work is to critically analyze the available data on the molecular targets of genistein in twelve different types of cancers, trying to identify common mechanisms of action of the molecule and its efficacy in enhancing chemotherapeutic protocols. In addition, depending on the data present in the literature on specific forms of cancers, e.g., breast cancer, we will try to highlight, not only the desired ("good") anticancer and chemopreventive effects of genistein, but also the unexpected and potentially dangerous consequences of its uses for treatment (Table 1).

2. Genistein

Many reports claim that consumption of soybean, because of the presence of genistein, reduces the risk of development of several types of cancer, including breast, prostate and colon cancer (Fournier, Erdman, & Gordon, 1998).

Search for the terms "genistein and cancer" in PubMed, reveals that the main molecular targets of genistein are estrogen receptors (ER), protein tyrosine kinases (PTK) and mammalian DNA topoisomerase II (Akiyama et al., 1987; Kuiper et al., 1998). Early reports have identified genistein as a potent inhibitor of PTK activity associated with epidermal growth factor receptor (EGFR), the designed target of Erlotinib, one of the first personalized drugs. A large part of these studies has focussed on the use of *in vitro* models and applied micromolar concentrations of genistein, revealing the "good" anticancer effects of the molecule. However, we are not only "what we eat", but essentially "what we absorb"; in other words, given the low plasmatic bioavailability of genistein (similar to other bioactive compounds present in the diet), it is necessary to distinguish between the potential chemopreventive effects of genistein (administered at low doses) and its pharmacological effect when administered at high doses. Essentially, the "bad" aspects of genistein, may derive from its *in vivo* effects which are strictly related to its circulating concentration.

We recently reviewed that the ability of genistein to inhibit cell growth (in both hormone-dependent and -independent cancer cells) is dose-dependent (Russo, Spagnuolo, Tedesco, & Russo, 2010; Spagnuolo et al., 2015). In fact, it has been reported that preferential activation of ERβ by genistein is lost when genistein is increased from low (6 nM) to higher concentrations. At hundreds nanomolar concentrations, genistein activated both ERs (α and β); therefore, the final effect on gene expression and cell fate depends on ligand dose and on the differential ability of ligand–ER complexes to recruit modulators at the ER binding sites of hormone-regulated genes (Chang et al., 2008). Reasonably, the antiproliferative activity of genistein at pharmacological doses (higher than 10 μM) is mediated by PTK inhibition, suggesting that genistein might exert *in vivo* anticancer effects.

In Fig. 2, several possible molecular targets of genistein are represented. The cartoon illustrates a key feature shared by several bioactive molecules, i.e., their "pleiotropic" activity, or the capacity