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Invited Review

The use of plant-derived bioactive compounds to target cancer stem cells and modulate tumor microenvironment

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ABSTRACT

In the last decades cancer has been considered as an epigenetic dysfunction, given the profound role of diet and lifestyle in cancer prevention and the determination of cancer risk. A plethora of recent publications have addressed the specific role of several environmental factors, such as nutritional habits, behavior, stress and toxins in the regulation of the physiological and cancer epigenome. In particular, plant-derived bioactive nutrients have been seen to positively affect normal cell growth, proliferation and differentiation and also to revert cancer related epigenetic dysfunctions, reducing tumorigenesis, preventing metastasis and/or increasing chemo and radiotherapy efficacy. Moreover, virtually all cancer types are characterized by the presence of cancer stem cell (CSC) subpopulations, residing in specific hypoxic and acidic microenvironments, or niches, and these cells are currently considered responsible for tumor resistance to therapy and tumor relapse. Modern anti-cancer strategies should be designed to selectively target CSCs and modulate the hypoxic and acidic tumor microenvironment, and, to this end, natural bioactive components seem to play a role. This review aims to discuss the effects elicited by plant-derived bioactive nutrients in the regulation of CSC self-renewal, cancer metabolism and tumor microenvironment.

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1. Introduction

It is broadly accepted that disruption of the epigenome is a critical hallmark of human cancers, contributing to cancer pathogenesis and progression. Epigenetic alterations normally occur early during the carcinogenic process, representing potentially initiating events in the development of cancer (Huang et al., 2011) (Schnekenburger et al., 2014). A fundamental aspect to be taken into account is that epigenetic changes can possibly be reversed by modifying epigenetic factors, such as diet and lifestyle. Nowadays, identification of these factors is crucial to develop epigenetically-based preventions and more effective anti-cancer intervention strategies.

Virtually, all dietary compounds have the ability to act at the epigenetic level in cancer cells thus influencing the epigenome in a positive or negative way. Particularly, plant derived compounds, such as polyphenols, have the capacity to reverse adverse epigenetic mutations in cancer cells, to inhibit tumorigenesis progression, to prevent the metastatic process or to sensitize cancer cells to chemo and radiotherapy (Vanden Berghe, 2012). Additionally, polyphenols, besides acting as antioxidant and anti-inflammatory compounds, can modulate transcription factors controlling the expression of genes involved in cell metabolism and survival, this having important implications for cancer growth control (Giampieri et al., 2014).

Natural food products have been shown to influence three crucial epigenetic processes, i.e. DNA methylation, histone modification and microRNA expression (Chen and Xu, 2010). Nevertheless, while diet-based interventions aiming to target epigenetic pathways are definitely promising, the translation of these scientific findings into clinical or public health practices still remains a challenging aspect (Chen and Xu, 2010).

In the last decades, many studies have highlighted the existence of cancer stem cells (CSCs) in many types of tumors, considered responsible for tumor relapse and resistance to chemo and radiotherapy (Al-Hajj et al., 2003; Bonnet and Dick, 1997; Li et al., 2007; O'Brien et al., 2007; Schatton et al., 2008; Singh et al., 2003; Yang et al., 2008), and novel therapeutic approaches effectively targeting the CSC pool are currently under investigation (Zhou et al., 2009).

It has been seen that CSCs, like embryonic and adult stem cells, are characterized by a self-renewal capacity and by the activation of a hyper-glycolytic metabolism, defined as aerobic glycolysis or Warburg effect (Lopez-Lazaro, 2008), together with a lowered mitochondrial respiration, compared to more differentiated and/or committed cells within the tumor bulk (Hammoudi et al., 2011; Liu et al., 2014; Palorini et al., 2014; Scatena, 2012; Yuan et al., 2013). In recent years many strategies have been designed to specifically target CSCs, such as inhibiting their self-renewal and chemoresistance related pathways, inducing their differentiation (Paldino et al., 2014; Persano et al., 2012; You et al., 2014), targeting some of their cell-surface molecular markers and ABC cassettes (Chen et al., 2013), impacting their metabolism via inhibition of glycolysis (Liu et al., 2014; Yuan et al., 2013) and/or by targeting mitochondria (Loureiro et al., 2013) and designing miRNA-based strategies to block cancer stemness (Bhardwaj et al., 2013; Yu et al., 2012).

Virtually in all tumors, CSCs seem to reside within specific microenvironments, or niches, characterized by the presence of hypoxia (Benito et al., 2013; Crowder et al., 2014; Mao et al., 2013; Pistollato et al., 2010), oxidative stress (Vera-Ramirez et al., 2012), the presence of chronic inflammation caused by a high level of cytokines (Shigdar et al., 2014; Tower, 2012) and an acidic pH (Catalano et al., 2013; Hjelmeland et al., 2011). Furthermore, extracellular matrix remodeling occurs in the cancer niche via the secretion of soluble factors and extracellular matrix components, critically contributing to cancer progression. The presence within the CSC microenvironment of oxidative stress and pro-inflammatory signals contributes to recruiting fibroblasts, endothelial and perivascular cells and to activating macrophages both in the peripheral tumor area and within the tumor mass. Consequentially, de novo angiogenesis occurs with the formation of new tumor vessels, possibly leading to tumor cell dissemination via the circulatory system (Catalano et al., 2013).

It is currently hypothesized that cancer can be overcome either by directly targeting CSCs (i.e. inhibiting their self-renewal and/or their metabolism) or by indirectly targeting the surrounding cancer niche (Ristow, 2006; Zhang et al., 2013). Here we revise current literature in this field, focusing on the beneficial effects of plant-derived compounds in the regulation of CSCs and the tumor niche.

2. Targeting CSC self-renewal with plant derived bioactive compounds

Several self-renewal related signaling pathways have been found to be deregulated in many cancer types (Harris et al., 2012; Takebe et al., 2011); for this reason, forcing CSCs into differentiation, reducing the stemness related phenotype, has been recently considered a potential strategy to reduce CSC proliferation (Paldino et al., 2014; Persano et al., 2012; You et al., 2014). Below we provide a revision of the most recent literature, addressing the role of plant-derived compounds in the regulation/inhibition of CSC self-renewal (Fig. 1).

It is known that natural dietary compounds can impact CSC self-renewal related pathways, such as Wnt/β-catenin, Hedgehog and Notch (Li et al., 2011). In particular, curcumin (CUR), present in the Indian spice turmeric, soy isoflavones, such as genistein (GEN), sulforaphane (SFN), indole-3-carbinol and 3,3′-diindolylmethane, found enriched in cruciferous vegetables, epigallocatechin-3-gallate (EGCG), present in green tea, resveratrol (RES), found particularly in red grapes and berries, lycopene, present in tomatoes, and piperine, present in black and long peppers, have been described to either directly or indirectly affect these self-renewal signaling pathways, contributing to the physiological regulation of normal (non tumorigenic) stem cells and also to the reduction of CSC growth (Li et al., 2011). Bioactive food compounds might also influence proliferation and quiescence by regulating dickkopf 1 (DKK-1), cyclin-dependent kinase 6 (CDK6), secreted frizzled-related protein 2 (sFRP2) and B cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1), and their effects seem to be elicited in virtually all organs and tissue types (Kim et al., 2012). Below the bioactive roles of some phytocompounds in relation to CSC biology are described, highlighting the molecular mechanisms underlying their effects on self-renewal related signaling pathways and CSC phenotype.

2.1. Effects of isothiocyanates (ITCs)

Isothiocyanates (ITCs), found especially in cruciferous vegetables, have been described for their positive effects in the prevention of human tumors (Zhang, 2004). The dietary consumption of ITCs seems to reduce the risk of developing several types of cancer, such as lung, breast and colon cancers (Zhang, 2004). ITCs