MINI-REVIEW

Multi-Target Cytotoxic Actions of Flavonoids in Blood Cancer Cells

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Abstract

To date, cytotoxic effects of flavonoids in various cancer cells are well accepted. However, the intracellular signaling cascades triggered by these natural compounds remain largely unknown and elusive. In this mini-review, the multiplicity of molecular targets of flavonoids in blood cancer cells is discussed by demonstrating the involvement of various signaling pathways in induction of apoptotic responses. Although these data reveal a great potential of flavonoids for the development of novel agents against different types of hematological malignancies, the pleiotropic nature of these compounds in modulation of cellular processes and their interactions certainly need unraveling and further investigation.

Keywords: Natural flavonoids - blood cancer cells - cytotoxic action - multi-targeted signaling - reactive oxygen species

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Introduction

The anticancer properties of flavonoids as plant secondary metabolites constituting an important part of the human diet are currently well accepted. Such activities include growth inhibitory effects, blocking the progression of cell cycle and inducing the death of malignant cells. At that, apoptosis or type I programmed cell death is the most common mechanism of chemotherapeutic as well as chemopreventive action of flavonoids (Baumann et al., 2008; Park et al., 2015). There are currently more than 5000 structurally different flavonoids and various molecular mechanisms can be underlying the cytotoxic effects exerted by these compounds in different cancer cells, including also blood cancer cells (Lu et al., 2007; Britschgi et al., 2010; Lanoue et al., 2010; Malyanto et al., 2012; Righeschi et al., 2012; Liu et al., 2015). Modulation of multiple cellular signaling processes by acting simultaneously on different molecular targets makes flavonoids novel attractive candidates for chemotherapy allowing to eradicate malignant cells and delay also the emergence of drug resistance (Spagnuolo et al., 2011; Benelli et al., 2012; Spagnuolu et al., 2012). However, the exact mechanisms by which flavonoids induce their cytotoxic activities in leukemia, lymphoma and myeloma cells have remained largely unclear and require certainly further investigation (Lu et al., 2007; Britschgi et al., 2010; Budhraja et al., 2012; Feng et al., 2012; Yuan et al., 2012). In this short communication, we present a brief overview of molecular targets of flavonoids in malignant blood cells and discuss the importance of such pleiotropic action in view of the development of novel antileukemia, antilymphoma and antimyeloma agents.

Multiple Targets of Flavonoids in Blood Cancer Cells

The proapoptotic activity of different flavonoids (the most common of them and more extensively studied: quercetin, fisetin, galangin, kaempferol, morin, myricetin, apigenin, luteolin, baicalein, wogonin, naringenin, genistein, as well as green tea catechins) in various blood cancer cells is related to the downregulation of antiapoptotic proteins, including Mcl-1, Bcl-2, Bcl-XL, and XIAP; and activation of proapoptotic proteins, including Bax, Bad, and Bid, cleavage of PARP and release of mitochondrial cytochrome c into the cytosol (see Figure 1) (Lee et al., 2002; Li et al., 2004; Ko et al., 2005; Shieh et al., 2006; Tolomeo et al., 2008; Han et al., 2009; Jin et al., 2009; Budhraja et al., 2012; Ghorbani et al., 2012; Switalska et al., 2013; Baran et al., 2014; Chen et al., 2015; Lee WS et al., 2015; Park et al., 2015). The generated imbalance in the expression of anti- and proapoptotic proteins increases the susceptibility of malignant cells to apoptotic signals and flavonoids induce apoptosis mostly through the caspase-dependent pathways, whereas both the mitochondrial (intrinsic) apoptotic cascade as well as death receptor-mediated (extrinsic) signaling can be activated (Ma et al., 2005; Lee et al., 2006; Lu et al., 2007; Lee et al., 2011; Chen et al., 2013).

Induction of cellular death pathways by flavonoids is often accompanied by the modulation of activity of different protein kinases (Figure 1); however, the exact mechanisms underlying these signaling cascades are still elusive and depend both on the certain flavonoids as well as the types of leukemia cells. In this respect, genistein is able to activate MAPKp38 and AMPK involved in

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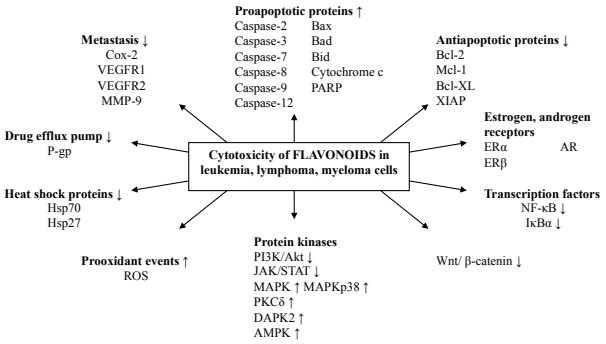

Figure 1. Pleiotropic Cytotoxic Activity of Flavonoids in Malignant Blood Cells. (Akt, protein kinase B; AMPK, AMP-activated protein kinase; AR, androgen receptor; Bad, Bcl-2-associated death promoter; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-XL, B-cell lymphoma-extra large; Bid, BH3 interacting-domain death agonist; Cox-2, cyclooxygenase 2; DAPK2, death-associated protein kinase 2; ER, estrogen receptor; Hsp, heat shock protein; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; Mcl-1, myeloid cell leukemia 1; MMP-9, matrix metalloproteinase 9; **NF-κB**, nuclear factor κB; PARP, poly(ADP-ribose) polymerase; P-gp, P-glycoprotein; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC, protein kinase C; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; VEGFR, vascular endothelial growth factor receptor; XIAP, X-linked inhibitor of apoptosis protein)

the apoptotic processes in U937 promonocytes and some other human leukemia cell lines (Sanchez et al., 2008). Also, quercetin can activate AMPK leading to the caspase-3-dependent apoptosis in HL-60 promyelocytes (Xiao et al., 2014). Green tea catechin EGCG enhances the programmed cell death signaling through an increase in DAPK2 protein in HL-60 and NB4 promyelocytes (Britschgi et al., 2010), while PKCδ represents a key player in apigenin-induced apoptotic response in THP-1 monocytes (Vargo et al., 2006). One of the major targets of apigenin seems to be also the JAK/STAT pathway that is downregulated in both myeloid as well as erythroid leukemia cells (Ruela-de-Sousa et al., 2010; De Martino et al., 2011).

Several blood cancer cells have shown to exert the characteristic of elevated level of phosphorylated Akt compared to their normal counterparts (Bortul et al., 2005; Yuan et al., 2012). Inhibition of PI3K/Akt pathway can play a crucial role in the apoptotic processes caused by multiple flavonoids in different blood cancer cells: by apigenin, quercetin and baicalin in HL-60 promyelocytes (Ruela-de-Sousa et al., 2010; De Martino et al., 2011; Yuan et al., 2012; Zheng et al., 2012); by quercetin, kaempferol, chrysin and deguelin in U937 promonocytes (Bortul et al., 2005; Ramos et al., 2008; Marfe et al., 2009; Khoo et al., 2010); by quercetin in chronic lymphocytic leukemia cells (Russo et al., 2014); by kaempferol, oroxylin A and wogonin in K562 myelogenous leukemia cells (Marfe et al., 2009; Wang et al., 2014; Xu et al., 2014); by baicalin in CA46 Burkitt lymphoma cells (Huang et al., 2012); by naringenin in THP-1 monocytes (Park et al., 2008); and by xanthohumol in several acute lymphocytic leukemia cells (Benelli et al., 2012). These flavonoids can behave as Akt inhibitors inducing the programmed cell death and may therefore have a strong potential as novel anticancer agents in the treatment of some hematological neoplasms.

Downstream of Akt, the constitutively higher activity of **NF-κB** can also be implicated in malignant transformation, whereas several flavonoids, like baicalein, deguelin and genistein are able to suppress the activity of this molecule (Chen et al., 2006; Otsuyama et al., 2007; Benelli et al., 2012; Yamasaki et al., 2013).

One important signaling cascade in cytotoxic responses triggered by flavonoids is considered to be the Wnt pathway that is blocked by quercetin in some leukemia cells like DND-41 T-lymphoblasts (Kawahara et al., 2009); however, these mechanisms are still rather poorly understood. Similarly, the involvement and precise role of several other molecular targets in flavonoids-induced cellular death, including estrogen and androgen receptors (Yamasaki et al., 2010; Sak et al., 2015), but also the heat shock proteins (Wei et al., 1994; Shen et al., 2008; Gonzalez-Mejia et al., 2010) definitely need further investigation (Figure 1).

Moreover, as depicted in Figure 1, flavonoids cannot only inhibit the proliferation of malignant cells and induce their death, but these compounds may also suppress the metastatic processes by modifying the interactions between blood cancer cells and the surrounding microenvironment (Benelli et al., 2012). For instance, several green tea catechins have shown to inhibit the expression of MMP-9, Cox-2 or VEGF receptors in different myeloid and lymphoid leukemia cells, being linked to suppression of inflammatory and angiogenetic processes and impeding thus the migration and invasion of neoplasms (Annabi et al., 2007; Angelo et al., 2009; Vezina et al., 2012; Harakeh et al., 2014).

ROS-dependent and -independent cytotoxicity

Among various mechanisms reported for the cytotoxic action of flavonoids (Figure 1), these compounds might exert their anticancer properties also through the prooxidant events, by promoting intracellular ROS generation (Sergediene et al., 1999; Ueda et al., 2001; Chen et al., 2004). Although flavonoids are generally known as antioxidants, they can act as prooxidants under certain conditions and the mitochondrial dysfunction pathway mediated by production of ROS is considered to play a pivotal role in the onset of cell death in several blood cancer cells. Indeed, the ROS increase is involved in apoptosis induction by quercetin, morin, tamarixetin, baicalein and baicalin in HL-60 promyelocytes (Wang et al., 1999; Wang et al., 2004; Kuo et al., 2007; Lu et al., 2007; Sakao et al., 2009a; Sakao et al., 2009b; Nicoloni et al., 2014); by quercetin in MOLT-4 lymphocytes (Mertens-Talcott et al., 2005); by baicalin in Jurkat T cells (Ueda et al., 2001); by EGCG in NB4 and UF-1 promyelocytes (Nakazato et al., 2005); and by eupatorin in some myeloid and lymphoid leukemia cells (Estevez et al., 2014).

However, the induction of programmed cell death can also occur independently on ROS production and this is reported even for the same flavonoids in similar cellular

context. On this point, quercetin has shown to trigger apoptosis in HL-60 promyelocytes also independently on its prooxidant effects (Shen et al., 2003) and myricetin, fisetin, casticin, wogonin, naringenin and hesperetin can also induce cytotoxic responses in HL-60 promyelocytes without promotion of ROS levels (Lee et al., 2002; Chen et al., 2003; Ko et al., 2005; Morales et al., 2012; Kikuchi et al., 2013). These somewhat contradictory data still need unraveling and the involvement of ROS in apoptotic machinery requires further clarification.

Conclusions and prospects

Numerous published reports clearly indicate that flavonoids can serve as novel therapeutic agents for treatment of different types of hematological malignancies. However, their signaling pathways in blood cancer cells have still remained elusive and it is evident that better understanding of the molecular targets and cellular mechanisms involved in the cytotoxic action of these natural compounds may contribute to the development of molecularly-targeted therapy for leukemia, lymphoma and myeloma. Simultaneous modulation of different signal transduction pathways can also be important to overcome the problems related to emergence of chemoresistance.

It is well known that flavonoids occur in the human diet in various combinations, whereas individual compounds interact with different molecular targets and simultaneously influence different intracellular signaling cascades. Therefore, the complex effects of bioactive constituents may reflect their synergistic action and this fact makes flavonoids especially attractive on view of the chemopreventive strategies. In the future, it would be tempting to study some of these combinations also from the therapeutic aspects to avoid the recurrence of different blood cancers and improve the patients` quality of life.

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