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Antidepressants: Influence on Cancer and Immunity?

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Abstract

Two decades ago, it was hypothesized that antidepressants could alter the course of neoplastic diseases. However, contradictory findings indicated that antidepressants could either have carcinogenic properties or improve the disease outcome. Intriguingly, controversial results were

reported on the action of antidepressant drugs on immune function. Further hypotheses proposed that antidepressants could indirectly affect the cancer prognosis through the modulation of antitumor activity. Here we review the literature in order to elucidate the influence of antidepressants on cancer and immunity.

Keywords: antidepressant; cancer; immunity; cytokines; cytotoxicity; fluoxetine; tumor proliferation; apoptosis

1. INTRODUCTION

Antidepressants are widely used to alleviate mood disorders, such as major depression and dysthymia (Stafford et al. 2001). These drugs alter either the reuptake of neurotransmitters at the synapse or the enzymes involved in their synthesis (Table 1). Additionally, antidepressants are often prescribed to cancer patients suffering from depressive episodes (Shuster et al. 1992). Epidemiologic evidence supports the role of biobehavioral factors, such as depression, in cancer progression (Lutgendorf and Sood, 2011). The pathways underlying this observation have been exhaustively discussed, and a recent comprehensive analysis proposed a unifying theory, involving chronic inflammation, activation of cell-mediated immunity, oxidative and nitrosative stress, reduction of antioxidants, damaged mitochondria structure and function, and neuroprogression (Maes et al. 2012). Interestingly, antidepressants are able to normalize the alterations observed in these pathways during depression (Maes et al. 2012). Moreover, a link between antidepressant use and cancer has been proposed (Cosgrove et al. 2011). Furthermore, the resistance to the immunomodulatory effects of antidepressants in some depressed patients may have an impact on tumor growth (Maes et al. 2012). It is plausible that at least some of these pathways may be directly modulated by antidepressants and could therefore be involved in the alteration of cancer progression. Here, we review the literature on the link between antidepressants and cancer, the role of the immune system, and the mechanisms involved in this interplay.

2. INFLUENCE OF ANTIDEPRESSANTS ON CANCER

Several clinical studies have indicated a link between antidepressant use and cancer. The nature of this association is discussed below.

2.1. Epidemiological studies on the influence of antidepressants on cancer prognosis

It was first proposed that antidepressants could increase the risk of cancer, with breast and colon cancers being the most studied malignancies. In breast cancer, an increased risk was suggested after the long-term use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) (Cotterchio et al. 2000; Moorman et al. 2003; Sharpe et al. 2002; Steingart et al. 2003). However, later studies consistently indicated that antidepressant treatment was not a concern for breast cancer patients (Ashbury et al. 2010; Coogan et al. 2005, 2008; Gonzalez-Perez and Garcia-Rodriguez, 2005; Tamim et al. 2006; Wang et al. 2001; Wernli et al. 2009). Moreover, women who used antidepressants after breast cancer diagnosis did not have an increased risk of recurrence or mortality (Chubak et al. 2008) Nevertheless, concerns regarding progesterone and estrogen receptors have not yet been fully addressed (Coogan et al. 2008; Chien et al. 2006).

Haukka et al. (2010) reported a bias in the association of antidepressants with a higher incidence of colon cancer. In fact, the regular use of SSRIs was associated with a reduced risk of colorectal cancer, likely through either an antipromoter or direct cytotoxic effect (Coogan et al. 2009; Xu et al. 2006). This observation was extended to TCAs, although in this case the reduced risk appeared to be limited to patients who had not had cancer previously (Chubak et al. 2011).

With respect to other types of cancer, it was first reported that psychotropic drugs, including antidepressants, could be associated with an increased risk of ovarian cancer (Harlow et al. 1995, 1998). However, further studies demonstrated no increased cancer risk among SSRI and TCA users (Coogan et al. 2000; Dublin et al. 2002; Moorman et al. 2005). SSRIs, but not TCAs, were associated with a reduced risk of lung cancer (Toh et al. 2007). TCA use was also associated with a small dose-dependent increase in the risk of prostate cancer, but detection bias could have

contributed to this association (Tamim et al. 2008). Dalton et al. (2000, 2008) reported an increased risk of non-Hodgkin's lymphoma, specifically among long-term users of TCAs. However, Bahl et al. (2004) found no association between antidepressant medication use and non-Hodgkin's lymphoma risk. Finally, TCAs may potentially prevent glioma in a specific and dose- and time-dependent manner (Walker et al. 2011). These heterogeneous data contemplate different antidepressants and types of tumors, but in general, antidepressants have an inhibitory effect on cancer prognosis.

2.2. Preclinical evidence of the effect of antidepressants on cancer prognosis in laboratory animals

Given the limitation of epidemiological studies, animal models have been used to study the effects of antidepressants on tumor progression. Desipramine was found to exacerbate azoxymethane-induced experimental carcinogenesis in the rat colon (Iishi et al. 1993). Additionally, fluoxetine and amitriptyline increased the proliferation of B16F10 melanoma cells and C3 fibrosarcoma cells grown in syngeneic animals (Brandes et al. 1992). Both drugs also enhanced mammary tumor growth in the chemical dimethylbenzanthracene (DMBA) induction model (Brandes et al. 1992). However, when fluoxetine was tested for carcinogenicity in rodents, significant decreases in a few commonly occurring neoplasms were found (Bendele et al. 1992). Moreover, fluoxetine also prevented colon cancer development in epithelial and stromal areas in rats (Kannen et al. 2011). Furthermore, fluoxetine inhibited PC-3 human prostate carcinoma in mice (Abdul et al. 1995). Finally, oral administration of 15 mg/kg of fluoxetine inhibited LBC lymphoma growth in syngeneic mice when administered before and/or after tumor graft, and it also improved the survival of the animals (Frick et al. 2008).

Additionally, sertraline inhibited A375 human melanoma and HT29 colorectal carcinoma growth in nude mice (Gil-Ad et al. 2008; Reddy et al. 2008). In the Emu-myc murine lymphoma model, where carcinogenesis is driven by phosphatase and tensin homologue (PTEN) inactivation, sertraline exacerbated chemosensitivity to doxorubicin (Lin et al. 2010). Clorgyline, an inhibitor of monoamine oxidase A (MAO-A), slowed tumor growth in the VCaP model of prostate cancer (Flamand et al. 2010). Conversely, the MAO-B inhibitor pargyline enhanced azoxymethane-induced experimental carcinogenesis in the rat colon (Iishi et al. 1994).

Interestingly, fluoxetine inhibited multidrug resistance extrusion pumps and enhanced responses to chemotherapy in syngeneic and human xenografted tumors in mice (Peer et al. 2004). Treatment of resistant colon cancer with a fluoxetine-doxorubicin combination enhanced therapeutic responses at a level comparable to an aggressive bevacizumab regimen (Argov et al. 2009). Similar results were obtained for clomipramine (Merry et al. 1991; Pommerenke and Volm 1995). Together, these results suggest that antidepressants primarily exert an inhibitory effect on tumor growth in animal models, which is consistent with the findings from epidemiological studies.

2.3. Effects of antidepressants on metastasis

Antidepressants may play a role in tumor metastasis. Brandes et al. (1992) found that rats receiving amitriptyline or fluoxetine develop more metastasis than the controls in the DMBA-induced mammary carcinogenesis model. Overall, desipramine and fluoxetine increased the metastasis of B16F10 melanoma in high- and low-active female and male mice (Kubera et al. 2011). Nevertheless, it is worth noting that this observation does not necessarily reflect the progression of the disease: desipramine increased tumor growth in low- and high-active females

but reduced tumor growth in males, while fluoxetine inhibited tumor growth in high-active males without affecting the other experimental groups (Kubera et al. 2011). It was also shown that, although desipramine inhibited primary tumor growth in young mice, it dramatically promoted metastasis formation and increased the mortality rate (Kubera et al. 2009a). However, desipramine and fluoxetine increased primary tumor growth in aged animals, whereas metastasis was only moderately promoted (Kubera et al. 2009a). Therefore, the association between antidepressants and metastasis and its relevance in malignant outcomes undoubtedly needs to be further studied.

2.4. Direct effects of antidepressants on cultured tumor cells

Brandes et al. (1992) reported that fluoxetine and amitriptyline can directly stimulate the proliferation of B16F10 melanoma cells and C3 fibrosarcoma cells in vitro. However, subsequent evidence strongly indicates an inhibitory action of antidepressants on tumor cells. Desipramine inhibited the growth of the Ca3/7 mouse skin squamous cell carcinoma (Kinjo et al. 2009). Additionally, amitriptyline, nortriptyline and clomipramine exerted activity against melanoma cells in vitro (Parker et al. 2012). Maprotiline and fluoxetine were found to have potent selective antiproliferative effects against Burkitt lymphoma (Cloonan et al. 2010). Additionally, imipramine, desipramine, amitriptyline and fluoxetine reduced the viability of human HT29 colon carcinoma cells (Arimochi and Morita, 2006). Finally, the sertraline- and paroxetine-induced inhibition of HT29 cells was associated with alterations in apoptosis-related proteins, suggesting that the tumor cells experienced programmed death (Gil-Ad et al. 2008). Therefore, evidence strongly indicates that antidepressants have a direct inhibitory effect on tumor cells.

2.5. Antidepressants as modulators of the cell cycle and apoptosis in cancer cells

Programmed cell death is the mechanism by which antidepressants are proposed to inhibit tumor growth. Imipramine, clomipramine and citalopram induced apoptosis in human acute myeloid leukemia HL-60 cells via caspase-3 activation (Xia et al. 1999a). Different SSRIs were found to trigger rapid and extensive programmed cell death on Burkitt lymphoma cells (Serafeim et al. 2003). A rapid increase in c-Jun phosphorylation, mitochondrial cytochrome-c release, and increased caspase-3 activity preceded paroxetine, fluoxetine and clomipramine-induced apoptosis in rat glioma and human neuroblastoma cells (Levkovitz et al. 2005). Desipramine induced apoptotic cell death through nonmitochondrial and mitochondrial pathways in human colon carcinoma cells (Arimochi and Morita 2008). Caspase-3 gene expression was also involved in desipramine-induced apoptosis of C6 glioma cells (Qi et al. 2002). In human osteosarcoma cells, desipramine and paroxetine induced apoptosis through p38 mitogen-activated protein kinase (MAPK)-associated activation of caspase-3 (Chou et al. 2007; Lu et al. 2009). In PC3 prostate cancer cells, desipramine caused apoptosis via c-Jun N-terminal kinase (JNK)-associated caspase-3 activation (Chang et al. 2008). Fluoxetine induced apoptosis in the ovarian carcinoma cell line OVCAR-3 through a decrease in cytosolic B-cell lymphoma 2 (Bcl-2) and BH3 interacting-domain death agonist (Bid) levels, an increase in mitochondrial Bcl-2–associated X protein (Bax) levels, caspase-3 activation and up-regulation of the p53 tumor suppressor protein (Lee et al. 2010). Interestingly, maprotiline and fluoxetine induced autophagic cell death in a chemoresistant lymphoma line and apoptosis in a chemosensitive line (Cloonan and Williams 2011). Similar results were found for imipramine and glioma cells (Jeon et al. 2011).

The cytotoxic effects of sertraline and paroxetine on Jurkat lymphoma cells included both the inhibition of proliferation and the induction of apoptosis (Amit et al. 2009). Desipramine altered

apoptosis and the cell cycle in vitro: Bcl-2, Survivin, and the cyclin-dependent kinase inhibitors p21 and p27 were overexpressed, whereas Bax, apoptotic protease activating factor (APAF)-1, caspase-3, caspase-7 and proliferating cell nuclear antigen (PCNA) were downregulated in skin squamous carcinoma Ca3/7 cells following antidepressant treatment (Kinjo et al. 2010). In lung and colon tumor cells, the antiproliferative effect of fluoxetine involved cyclin A, cyclin D1, p21 and p53 (Stepulak et al. 2008). Similarly, fluoxetine-mediated G0/G1 arrest was dependent on the inhibition of cyclin-dependent kinase subunit (CKS)-1 in cervical and breast cancer; and p27, p21, cyclin A and cyclin E were implicated in this cytostatic effect, which also potentiates cyclophosphamide action (Krishnan et al. 2008). Amitriptyline arrested myeloma cells at the G0/G1 phase of the cell cycle reducing cyclin D2 expression, activating caspase-3, and increasing p27 and p21 expression (Mao et al. 2011). Therefore, antidepressants are not only capable of inducing apoptosis in tumor cells, but they can also arrest the cell cycle (Figure 1). Furthermore, similar effects were observed in vivo: fluoxetine administration to lymphoma-bearing mice resulted in increased apoptotic cells (active caspase-3^{+}) and decreased proliferative cells ($PCNA^{+}$). Reductions in Bcl-2, cyclin D3, E and B expression and increases in p53, p15, p16, p27 and Bcl-2-associated death promoter (Bad) expression were also observed in tumor cells (Frick et al. 2011).

2.6. Antidepressants as modulators of oxidative and nitrosative pathways

Importantly, antidepressants are related to antioxidant responses, oxidative and nitrosative stress, suggesting possible implications for cancer progression. Amitriptyline, imipramine, fluoxetine and tranylcypromine caused pivotal alterations in the intracellular levels of reduced glutathione (GSH) in glyoma and astrocytoma cells (Slamon and Pentreath 2000). The induction of apoptosis by imipramine, clomipramine and citalopram in myeloid leukemia cells was preceded by the

hypergeneration of intracellular reactive oxygen species (ROS) and the loss of mitochondrial membrane potential (ΔΨm) (Xia et al. 1999a, 1999b). Moreover, amitriptyline not only induced high levels of ROS and irreversible mitochondrial damage, but it also decreased the antioxidant machinery in lung, cervical and liver tumor cells (Cordero et al. 2010). Bupropion induced endoplasmic reticulum stress and mitochondrial cytochrome-c release in a neuroblastoma cell line (Jang et al. 2011). Fluoxetine also improved cancer prognosis in vivo through antioxidant properties, modulating the melanoma-induced oxidative changes in the spleen, and the activity of cerebral superoxide dismutase (SOD) levels in hepatoma-bearing mice (Kirkova et al. 2010; Qi et al. 2009).

3. IMMUNOMODULATORY ACTION OF ANTIDEPRESSANTS

In recent decades, increasing evidence has revealed that antidepressants can modulate immune function. Surprisingly, a direct effect of antidepressants on non-neural cells has been described in vitro. The literature available in this field is discussed below.

3.1. Direct effects of antidepressants on the immune system

The direct effects of antidepressants on immunity have been demonstrated by in vitro assays, are independent of the central nervous system, and are proposed to be mediated by neurotransmitter transporters expressed by lymphoid cells (Gordon and Barnes 2003). SSRIs increase natural killer (NK) cell activity from healthy subjects, however TCAs inhibit NK cell activity (Frank et al. 1999; Xiao and Eneroth 1996). Imipramine, clomipramine and citalopram induced apoptosis in human peripheral lymphocytes, and cytotoxic T-lymphocytes were found to be more sensitive than T-

helper cells (Karlsson et al. 1998; Xia et al. 1997, 1998). These antidepressants also inhibited the differentiation of human monocytes into macrophage-like cells in vitro (Ying et al. 2002). Fluoxetine also suppressed the ability of dendritic cells to present bacterial antigens to T cells, due to diminished expression of costimulatory molecules (Branco-de-Almeida et al. 2011).

Antidepressants also modulate the production of cytokines by immune cells. Imipramine and venlafaxine increased interleukin (IL)-6 production by human blood cells from healthy donors in vitro (Kubera et al. 2004). In contrast, fluoxetine decreased tumor necrosis factor (TNF)-α production (Maes et al. 2005). Clomipramine, imipramine and citalopram also inhibited IL-6, IL-1β and TNF-α release by human blood monocytes and IL-2 and interferon (IFN)-γ release by T cells (Xia et al. 1996b). Moreover, it was demonstrated that IFN-γ-producing T_H1 cells are the major target of the immunomodulatory actions of antidepressants (Diamond et al. 2006). Interestingly, diverse antidepressants belonging to different families, such as imipramine, venlafaxine, fluoxetine, clomipramine, sertraline and trazodone, consistently reduce the IFN-γ/IL-10 ratio (Kubera et al. 2001, 2009b; Maes et al. 1999). The antidepressant-induced alteration of cytokine production is related to immune function. Paroxetine, sertraline and clomipramine reduced TNF-α production and the viability of rat splenocytes and human T lymphocytes (Taler et al. 2007, 2008). Amitriptyline affected the viability of purified epidermal Langerhans cells and peritoneal macrophages, as well as TNF-α and IL-12 production (Campelo et al. 2011).

Interestingly, fluoxetine exerts a dual effect upon in vitro T cell proliferation that depends on the degree of lymphocyte activation: at optimal concanavalin concentrations, fluoxetine had an inhibitory effect on cellular proliferation, whereas at submitogenic concentrations, fluoxetine stimulated lymphocyte reactivity (Edgar et al. 1998, 1999; Frick et al. 2008). The stimulatory effect on T cells was only achieved at low concentrations, ranging from 10^{-6}M to 10^{-8}M, while the effect

became inhibitory at a high dose of 10^{-5}M (Edgar et al. 1998, 1999; Frick et al. 2008). A similar effect was observed for splenocyte proliferation induced by anti-immunoglobulin M antibodies: in the presence of 10^{-6}-10^{-7}M of fluoxetine, sub-mitogenic stimulation increased B cell proliferation, and optimal mitogen concentrations inhibited proliferation (Genaro et al. 2000).

These findings raise the question of whether the inhibitory effects observed in vitro with high doses of antidepressants are only due to nonspecific toxicity. The toxic effect of fluoxetine on neutrophils was observed at high (10^{-3}/10^{-4}M) but not at low (10^{-5}/10^{-6}M) concentrations (Ploppa et al. 2008; Strümper et al. 2003). The same dose-response was reported for other types of antidepressants, namely nortriptyline, amitriptyline and imipramine (Ploppa et al. 2008; Strümper et al. 2003). Moreover, clomipramine, sertraline or paroxetine failed to alter the viability of splenocytes and T lymphocytes at 10^{-6}/10^{-7}M, but at 10^{-5}M they were able to trigger apoptosis in these cells (Taler et al. 2007, 2008). Therefore, it is plausible that the inhibitory effects observed with high doses of antidepressants could be due to nonspecific toxicity, as discussed below.

3.2. Systemic action of antidepressants on the immune system of laboratory animals

Pellegrino and Bayer (1998, 2000, 2002) reported that acute, but not chronic, fluoxetine administration decreases mitogen-induced T lymphocyte proliferation and NK cytolytic activity. Conversely, prolonged oral administration (4 weeks) of 15 mg/kg fluoxetine enhanced T cell proliferation in mice, and this was accompanied by increases in IL-2, IFN-γ and TNF-α without affecting NK and B cell activity (Frick et al. 2008, 2009). In rats, chronic administration of fluoxetine increased the number of T lymphocytes that express the serotonin transporter, reduced the $CD4^+$ /$CD8^+$ ratio, and increased the production of IL-4 and IL-2 (Fazzino et al. 2009).

Chronic amitriptyline administration increased NK cell cytotoxic activity, whereas acute maprotiline injection suppressed murine NK cell function (Eisen et al. 1989; Kubera et al. 1995). Moreover, citalopram and fluoxetine stimulated the proliferative activity of splenocytes, suppressed their ability to secrete the anti-inflammatory cytokine IL-4, but increased the secretion of IL-6 and IL-10 (Kubera et al. 2000a). Additionally, desipramine and amitriptyline also stimulated the proliferative activity of splenocytes and the secretion of IL-10; however, differential effects were reported: only desipramine reduced IL-4 and increased IL-1, whereas only amitriptyline increased IL-2 (Kubera et al. 2000b). In contrast, repeated mirtazapine administration suppressed the proliferation of splenocytes and their ability to produce pro-inflammatory cytokines, whereas it stimulated IL-4 production (Kubera et al. 2006). Thus, a large number of studies indicate a stimulatory rather than an inhibitory effect of antidepressants on the immune system.

Oral administration of 10-25 mg/kg fluoxetine in mice results in plasma concentrations of approximately 170-1780 ng/ml, which correspond to $5x10^{-7}$M-$5x10^{-6}$M (Dulawa et al. 2004). Serum fluoxetine levels achieved with the dose used in vivo by Frick et al. (2008, 2009) are within the range of plasmatic levels found in patients taking 20-80 mg/day Prozac (100-700 ng/ml); the equivalent values in human serum are approximately $2x10^{-7}$M-$3x10^{-6}$M (Koran et al. 1996). Thus, the systemic enhancement of T cell immunity is consistent with the in vitro stimulation of T cell proliferation at low fluoxetine concentrations, ranging from 10^{-6}M to 10^{-8}M (Edgar et al. 1998, 1999; Frick et al. 2008). Therefore, it is plausible that antidepressants have a stimulatory effect on immune cells under physiological conditions, emphasizing the importance of the dose range for cell culture studies. In fact, at a concentration of 10^{-6}M, fluoxetine increases NK cell activity (Frank et al. 1999). Thus, high antidepressant concentrations do not necessarily mirror the conditions occurring in vivo and may be not relevant for the translation from cell culture to preclinical studies.

3.3. Intracellular signal transduction of antidepressant action on immune cells

The mechanisms underlying the immunomodulatory action of antidepressants are largely unknown; nevertheless, some of the intracellular pathways involved have been identified (Figure 1). For instance, fluoxetine modulated T cell function through protein kinase C (PKC) and protein kinase A (PKA), involving cyclic adenosine monophosphate (cAMP) production and Ca^{2+} mobilization (Edgar et al. 1998, 1999; Maes et al. 2005). In human lymphocytes, c-Myc contributed to antidepressant-induced apoptosis, likely through Fas-mediated signaling (Xia et al. 1996a). Furthermore, the signal transducer and activator of transcription (STAT)-3 and the MAPK signaling pathway were involved in the actions of paroxetine, sertraline and clomipramine on rat splenocytes and human T lymphocytes (Taler et al. 2007, 2008). The signaling pathways involved still need to be further studied.

4. LINKING ANTIDEPRESSANTS TO ANTITUMOR IMMUNITY AND CANCER PROGNOSIS

An interesting hypothesis is that antidepressants can modulate tumor progression by an indirect action on antitumor immunity (Figure 2). Eisen et al. (1989) have associated in vivo NK cell function with tumor clearance from the lung upon chronic maprotiline treatment. B16F10 melanoma growth was associated with the production of IL-6, IL-10 and IL-12p40 in fluoxetine-treated mice (Kubera et al. 2009a). Moreover, fluoxetine inhibited lymphoma growth through an increase in $CD8^+$ cytotoxic cells as well as IFN-γ and TNF-α levels (Frick et al. 2011). Finally, mirtazapine inhibited colon carcinoma growth through the enhancement of circulating IL-12 levels, intra-tumor IFN-γ concentrations and infiltrating $CD4^+/CD8^+$ T cells (Fang et al. 2012).

Therefore, there is a link between the immune system and the antidepressant-induced alterations in tumor growth. This key role of antidepressants on the immune system as a mediator of cancer suppression is also supported by the lack of an effect of fluoxetine on tumor growth in athymic mice (devoid of T lymphocytes) even after prolonged treatment (Frick et al. 2008). Antidepressants may not only modulate tumor growth by altering cellular activity, but may also act through the oncostatic activity of cytokines. For instance, IL-6 is an important mediator of antitumor responses against melanoma (Sun et al. 1992), TNF-α is a potent effector against lymphomas (Krawczyk et al. 1995), and IL-12 has antitumor and antimetastatic properties against murine tumors (Brunda et al. 1993). Thus, a connection between the effect of antidepressants on cytokines and the described oncostatic action can be established.

One exciting possibility could be that antidepressants modulate the balance between T_H1 and T_H2 cytokines in tumor-bearing animals, thus promoting antitumor immunity. Although few works are available, Kubera et al. (2009a) reported a decrease of the T_H2 cytokines IL-6 and IL-10 in desipramine-treated mice that had previously been injected with B16F10 melanoma, and they concluded that this was related to the inhibition of tumor growth and improved survival in young animals. Conversely, lymphoma-bearing animals treated with fluoxetine and colon carcinoma-bearing mice treated with mirtazapine displayed a reduction in tumor growth in parallel with an increase in the T_H1 cytokines IL-12 and IFN-γ (Fang et al. 2012; Frick et al. 2011). The balance between T_H1 and T_H2 cytokines has been implicated in the elimination of tumor cells (Kidd, 2003). Therefore, the differential modulation of pro- and anti-inflammatory cytokines could be involved in the antidepressant-mediated inhibition of tumor growth, most likely by an increase in the T_H1/T_H2 ratio.

5. CONCLUDING REMARKS

The epidemiological and preclinical studies compiled in this review indicate a predominantly inhibitory action of antidepressants on cancer prognosis. Although some reports suggest an association of antidepressants with an increased risk of cancer, these differences may rely on the type of cancer and the antidepressant tested. As a future direction, it will be necessary to perform further studies examining these two parameters. Additionally, studies have clearly shown that the direct action of antidepressants on tumor cells is oncostatic. Interestingly, antidepressants seem to exert their control of cancer progression through a mechanism involving the modulation of the cell cycle and apoptosis in tumor cells.

Antidepressants have been shown to modulate immune function. However, when taken together, the observations of direct activity by antidepressants on lymphoid cells and the overall effects of systemic drug administration are not quite conclusive. For in vitro analyses, some studies using low concentrations of antidepressants indicate a stimulatory effect upon immune cells, whereas a considerable number of the reports found a direct immune-suppressant action of these drugs. Conversely, in vivo studies, comprising systemic administration of antidepressants into laboratory animals, indicate a consistent immune-stimulatory effect. However, the high doses used in several in vitro studies do not represent the blood levels of antidepressants achieved after systemic administration in vivo. The limited relevance of high doses of antidepressants on direct immunosuppression in vitro must be taken into account when comparing the effects of these drugs to data acquired at physiological conditions. Finally, although the mechanism of action of antidepressants seems to be the modulation of immune function, as evidenced by the alterations of cell signal transduction, the complete story needs to be elucidated.

To conclude, antidepressants may act to control tumor growth by reducing the malignant cell cycle, and their ability to activate the immune system may induce apoptosis in tumor cells. It is worth noting that the majority of the studies that are available in the literature specifically examine the effects of fluoxetine, which is the most widely prescribed antidepressant. It is indeed tempting to extrapolate these findings to other similar drugs. However, it is indispensable to deeply investigate each antidepressant in the future.

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Figure 1. Regulation of cell cycle, signaling and death by antidepressants. In tumor cells, apoptotic death triggered by antidepressants is mediated by cytochrome-c (CytC) release from the mitochondria, the apoptotic protease activating factor (APAF)-1 complex and caspase activation, downregulation of B-cell lymphoma 2 (Bcl-2) and BH3 interacting-domain death agonist (Bid), and upregulation of Bcl-2-associated X protein (Bax) and Bcl-2-associated death promoter (Bad). On the other hand, antidepressants also block cell cycle progression through the cyclin-dependent kinase inhibitor proteins p15, p16, p21 and p27, and inhibiting cyclins B, D1, D2, D3 and E expression. Apoptosis and proliferation might be inter-connected by the tumor suppressor p53, which regulates cell cycle through p21 but also unblocking survivin-mediated control of apoptosis. The molecular targets of antidepressants remain unknown, but these drugs might act on serotonin (5-HT), dopamine (DA) and/or norepinephrine (NE) signaling. So far, Ca^{2+} and cyclic adenosine monophosphate (cAMP) are the only second messengers that have been identified in lymphocytes, where antidepressants could act on neurotransmitter transporters expressed in the cell surface. The Fas-Fas ligand pathway was also identified as a mechanism of action in lymphocytes, and cytokines may also regulate apoptosis through signal transducer and activator of transcription (STAT3). Several kinases are involved in the action of antidepressants: protein kinase C (PKC) and protein kinase A (PKA) in immune cells, c-Jun N-terminal kinase (JNK) in tumor cells, and mitogen-activated protein kinase (MAPK) in both cell types. Regulation of kinase activation by antidepressants leads to altered phosphorylation of the oncogenes Myc and Jun, affecting cell proliferation. Additionally, MAPK and JNK activate caspase 3 to trigger apoptosis probably in an indirect manner.

Figure 2. Control of tumor growth by antidepressants. Antidepressants can control tumor growth by two mechanisms. First, antidepressants can trigger apoptosis in cancer cells and inhibit cell proliferation. Second, antidepressants may control antitumor immunity by means of enhancing cytotoxic activity against cancer cells and by modulating the production of T_H1 and T_H2 cytokines.

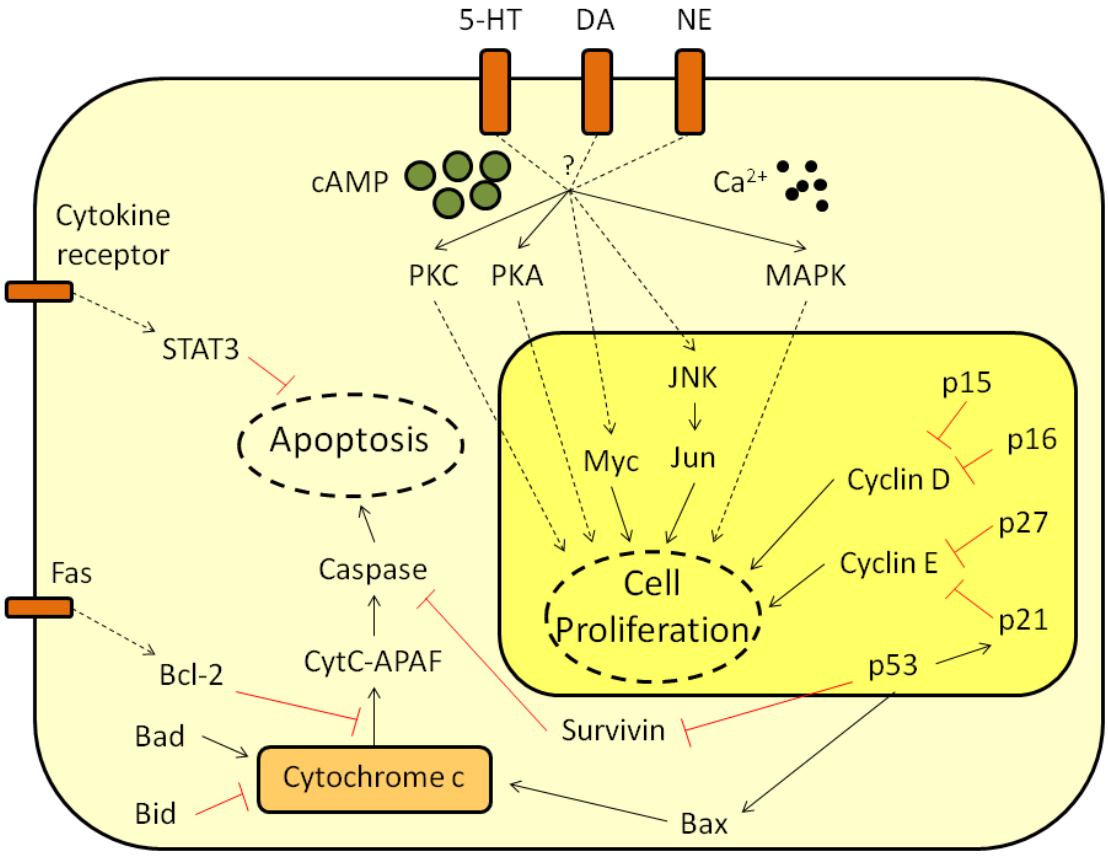


Figure 1

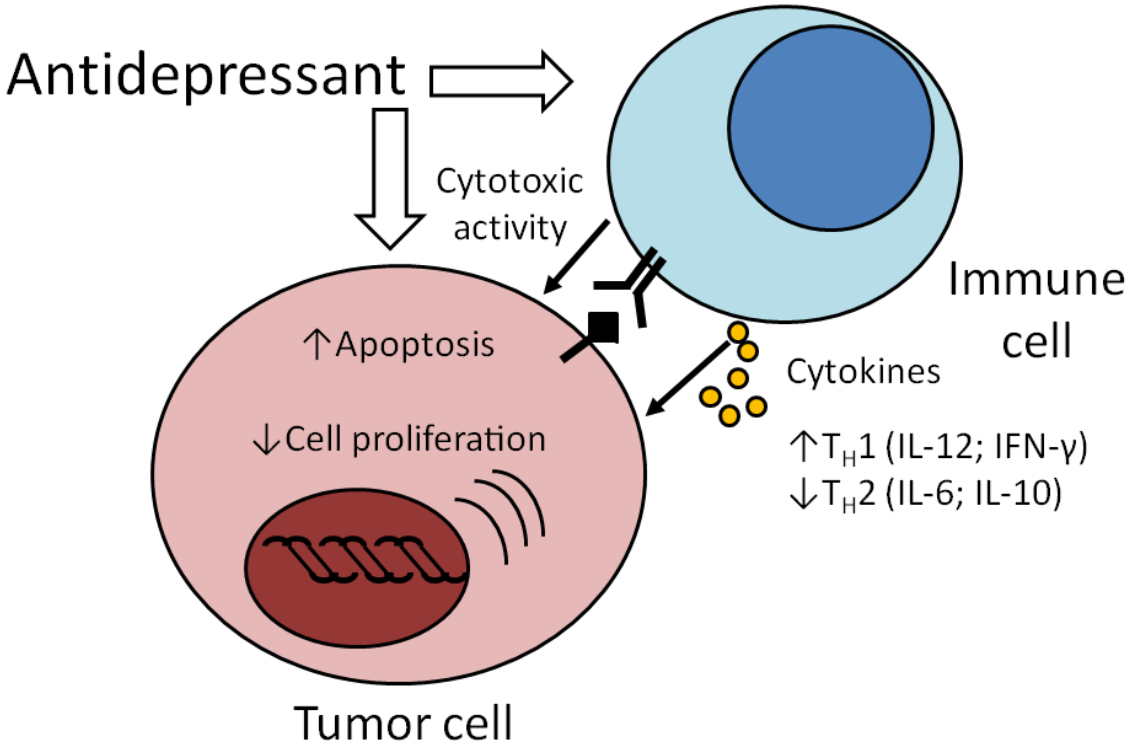
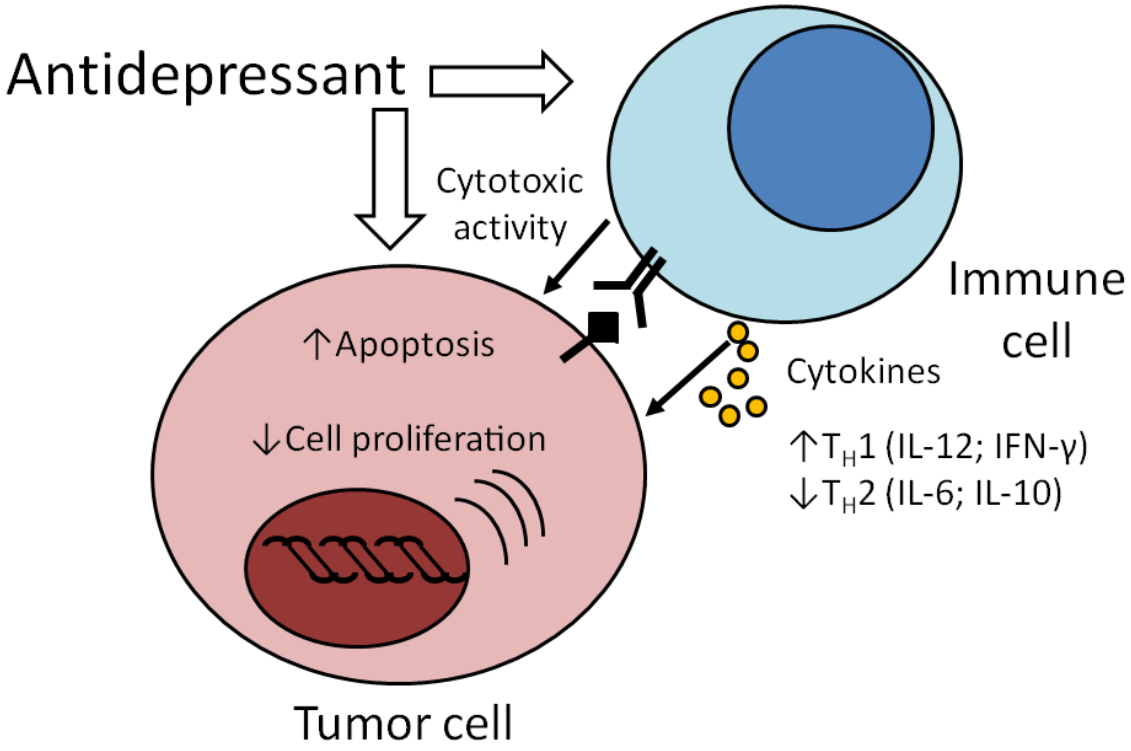


Figure 2

Classification	Antidepressants
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram; fluoxetine; paroxetine; sertraline
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine
Norepinephrine reuptake inhibitors (NRIs)	Maprotiline
Noradrenergic and specific serotonergic antidepressants (NaSSA)	Mirtazapine
Norepinephrine-dopamine reuptake inhibitors (NDRIs)	Bupropion
Tricyclic antidepressants (TCAs)	Amitriptyline; clomipramine; desipramine; imipramine; nortriptyline
Monoamine oxidase inhibitor (MAOI)	Clorgyline; pargyline; tranylcypromine
Serotonin antagonist and reuptake inhibitor (SARI)	Trazodone

Table 1. Antidepressants cited in this minireview and their classification by mechanism of action and/or structure. The antidepressants maprotiline and mirtazapine are classified as Tetracyclic antidepressants (TeCAs) according to their chemical structure. TCAs are predominantly serotonin and/or norepinephrine reuptake inhibitors.



Graphical abstract