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RESEARCH ARTICLE

Pesticide dichorvos induces early solid Ehrlich tumoral development associated with a non-protective pro-inflammatory response

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Abstract

Prolonged exposure to dichlorvos (DDVP), a common pesticide used for food crops, has been related to the development of infections and malignancies. Macrophages are used as bioindicators of immunotoxicity; thus, evaluation of their activity in solid Ehrlich tumor-bearing mice (TBM) may be useful to evaluate the influence of pesticides on human health. To investigate the effects of low DDVP doses, Swiss mice were divided into the following groups: the DDVP group, composed of mice fed diets containing 10 mg/kg of DDVP; the TBM group, consisting of mice subcutaneously inoculated with 10^7 tumor cells/100 μl and fed a basal diet; the DDVP-TBM group, consisting of mice previously fed DDVP-containing diets for 28 days and then subcutaneously inoculated with tumor cells; and the control (CTRL) group, composed of mice fed a basal diet. After 7 and 21 days of tumor inoculation, the mice were euthanized; and after necroscopic examination, the neoplastic mass, organs, and intraperitoneal fluid were collected. Adherent peritoneal cells were cultivated to determine the production of H_2O_2 and TNF. Altogether, our results indicate that even at low doses, the intake of DDVP caused weight loss and increased tumor mass, which were associated with H_2O_2 production and high levels of TNF, a pro-inflammatory cytokine. These data are important as the exposure to pesticides, even at low doses, could potentially hinder the immune response against tumors and, consequently, create favorable conditions for their development.

Keywords Dichorvos · Macrophage activity · Ehrlich tumor · Cytokines · Immunotoxicity · Organophosphorus

Introduction

According to the Food and Agriculture Organization of the United Nations (FAO), pesticides are substances intended for preventing, destroying, or controlling pests. These substances pose a serious risk to human health, since they are released in large quantities into the environment, and some of them can persist and bioaccumulate in the food chain (FAO 2003; Galloway 2003; ANVISA 2008). Large-scale use of these products is responsible for contaminating water, soil, and air, exposing more people to their toxic effects, and Brazil is the main consumer of pesticides in the world (Souza et al. 2017). Between 2000 and 2012, the cumulative growth of pesticide use in Brazil was higher than the overall productivity of crops (Almeida et al. 2017). Acute pesticide poisonings rank third among the causative agents of human disorders in Brazil, and the organophosphate (OP) insecticide class was responsible for about 73% of these cases (Oga 2008). Among the organophosphorus compounds used in food crops, dichlorvos (DDVP or 2,2-dichlorovinyl dimethyl phosphate) is a pesticide capable of altering functions of the immune system, facilitating the development of opportunistic infections and malignancies (Ivanovic-Matic et al. 2008). DDVP affects several host defense mechanisms such as antibody production, proliferation of the T cell-dependent complement system, and neutrophil and macrophage activity (Li et al. 2007; Vial et al. 1996). Despite these alterations, the effect of low doses of DDVP on the immune system during tumor development is still unclear.

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The pesticide-host relationship exhibits complex mechanisms, and macrophages have emerged as crucial immune cells involved in these processes because they act in several stages of tissue response, including the production of mediators for cellular recruitment, phagocytosis of microorganisms, release of cytotoxic enzymes, polarization of adaptive immune response, and would healing (Descotes 2006). Furthermore, macrophages have been used as bioindicators of immunotoxicity as they comprise diversified immune cell subsets. Additionally, depending on the context, they may act as pro- or anti-tumoral elements (Stout and Suttles 2004; Barnett and Brundage 2010). In addition to natural breakdown by the environment, xenobiotic degradation processes can also occur through enzymatic reactions, severely affecting the human body and its systems (Barnett and Brundage 2010).

Our group has previously reported that the solid Ehrlich tumor, a spontaneous breast cancer originating in mice, does not heal spontaneously (Dagli et al. 1992), progresses over time to an immunosuppressive phenotype that, after 21 days, fails to yield an effective response against fungi (Camargo et al. 2009). These effects were associated with changes in the oxidative metabolic activity of peritoneal adherent cells (PACs), with decreased pro-inflammatory cytokines tumor necrosis factor (TNF) and interferon (IFN)-ɣ, typical M2-like macrophage polarization, and the persistence of opportunistic infections (Camargo et al. 2009; Venturini et al. 2009). Thus, the Ehrlich tumor-bearing mice are interesting models to evaluate if early exposure to pesticides could increase tumor progression.

Considering this, we assessed the possible impacts of exposure to low-dose DDVP on Ehrlich tumor-bearing mice, mimicking the effects in cancer patients who may also be exposed to pesticides through food consumption.

Materials and methods

Animals Two-month-old male Swiss mice from the UNESP Animal Facilities at the Laboratorio de Imunopatologia Experimental (LIPE) of UNESP/Universidade Estadual Paulista, Bauru, SP, Brazil were housed in groups of three to five mice and were provided food and water ad libitum. All protocols used were in accordance with the ethical principles for animal research adopted by the Brazilian College of Animal Experimentation (COBEA). The basal chow (Rhoster Indústria e Comércio Ltda, Vargem Grande Paulista, SP) was produced to ensure its formulation was free of residues of pesticide constituents.

Ehrlich solid tumor (EST) This mammary tumor does not resolve spontaneously in mice. It may evolve to an ascitic (EAT) or solid form depending on the route of inoculation (intraperitoneal or subcutaneous, respectively). In this study, the tumor was maintained in the ascitic form in Swiss mice, and the cells were collected according to Silva et al. (2002). Tumor cells (10^7/100 μl) were inoculated subcutaneously into both the TBM and DDVP-TBM groups.

Experimental design Forty-eight mice were divided into four groups: the DDVP group was composed of mice fed diets containing 10 mg/kg/day of DDVP (LEL; lowest effective level – OECD 1995; OECD 1998); the TBM group was composed of mice subcutaneously inoculated with 10^7 tumor cells/100 μl and fed a basal diet; the DDVP-TBM group consisted of mice previously fed a DDVP-containing diet for 28 days prior to subcutaneous inoculation with tumor cells; the CTL group was composed of mice treated with basal diet. The mice were clinically evaluated weekly. Seven or 21 days after tumor inoculation, the mice were euthanized, and after necroscopic examination, the neoplastic mass and intraperitoneal fluid were collected. The PACs were cultivated to determine the production of hydrogen peroxide (H_2O_2) and TNF.

Collection of biological material Mice were euthanized in a CO_2 chamber. Fragments of the tumor mass, liver, spleen, and kidneys were collected, conditioned in 10% formalin, and processed for histological analyses by routine procedures for paraffin embedding and hematoxylin and eosin (H & E) staining.

Intraperitoneal lavage Macrophage activity was evaluated by PAC culture. For this, peritoneal cells were collected by washing the peritoneal cavity with 10 ml ice-cold sterile phosphate buffered saline (PBS), pH 7.4. The suspension was centrifuged, and the cells were resuspended in 1 ml RPMI-1640 (Cultilab, Campinas, SP, Brazil) containing 10% heat-inactivated fetal calf serum (Gibco BRL, Grand Island, NY, USA). The cell concentration was adjusted to 2×10^6 peritoneal macrophage-like cells/ml, as judged by the uptake of 0.02% neutral red. The peritoneal cells were placed in 96-well flat-bottom microtiter plates (Costar, Cambridge, MA, USA) and incubated for 2 h at 37 °C and 5% CO_2 in a humidified chamber to allow cell adherence and spread. Non-adherent cells were removed by washing the wells three times with RPMI, and the remaining adherent cells (> 97% macrophages as assessed by morphological examination and expression of F4/80 by FACS) were used for experiments. PACs were cultured at 37 °C, 5% CO_2, in RPMI-1640 with or without 10 μg/ml LPS (Sigma) as an internal control for macrophage activity (data not shown). After 24 h, the cell-free supernatants were harvested and stored at −70 °C pending cytokine analysis.

H_2O_2 release At the end of the culture period, the supernatant was removed; and adherent cells were incubated with phenol

red solution [dextrose (Sigma), phenol red (Sigma), and horseradish peroxidase type II (Sigma)] and plated at 37 °C in 5% CO_2 for 1 h according to the methods of Russo et al. (1989). The reaction was stopped with the addition of 1 N NaOH, and the H_2O_2 concentration was determined using an ELISA microreader.

Cytokine analysis The levels of TNF were measured in the cell-free supernatants of the cell cultures using a cytokine Duo-Set Kit (R&D Systems, Minneapolis, MI, USA), according to the manufacturer's instruction. Each sample was analyzed in duplicate.

Statistical analysis Data were analyzed using the Mann-Witney method. All statistical tests were conducted using GraphPad InStat version 3.0 for Windows (GraphPad Software, San Diego, California, USA), and a two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

DDVP intake triggers pro-tumoral macrophage activity

In the present study, we first evaluated if the intake of DDVP modifies the ability of PACs to produce mediators during tumor progression. For this, we quantified the production of H_2O_2 for 7 and 21 days of tumor progression. The results showed that in DDVP-TBM mice, this parameter was biphasic, presenting a significant increase in the production of H_2O_2 7 days after tumor inoculation (Fig. 1a) in relation to other groups, and a drop in production at day 21 (Fig. 1b).

Likewise, mice in the DDVP-TBM group showed significantly high levels of TNF production on day 7, and this production increased until the last study period (Fig. 2a). This increase was also observed in animals of the DDVP group (Fig. 2b), suggesting that the pesticide itself has an important pro-inflammatory action.

DDVP induces early tumor progression and weight loss

TNF has also been associated with the onset of systemic inflammation. According to the literature, continuous and prolonged exposure of the body to this cytokine can lead to cachexia. The results obtained in this study support this assumption, since at the end of 21 days, the tumor-bearing animals fed pesticide diet (DDVP-TBM) showed a significant decrease in body weight compared to animals in the other groups (Fig. 3a, b). However, other parameters need to be evaluated to confirm a cachexic condition in this study.

Moreover, when analyzed separately, the tumor weight of animals in the DDVP-TBM group was significantly higher than that of the animals not exposed to the pesticide (Fig. 4a, b).

Discussion

DDVP is an OP pesticide that is widely used worldwide (Oliva et al. 2003), but toxicological studies involving phagocytes and DDVP are still lacking, especially at low doses. Macrophages are key components of cellular immune responses and inflammation; they are involved in antigen processing and presentation to lymphoid cells and are responsible for H_2O_2 release and TNF production, which are essential parameters for the analysis of macrophage activity in response to toxicants (Barnett and Brundage 2010; Muller and Dieterle 2009; Righi and Palermo-Neto 2005).

In our study, we showed that at low doses, no significant changes were observed in the liver, kidney, or spleen, similar to the findings of Camargo et al. 2013 who showed that short-term exposure to low-doses of dieldrin, dichlorvos, dicofol, endosulfan, or permetrin pesticides, individually or in combination, did not alter peritoneal macrophage activity or the

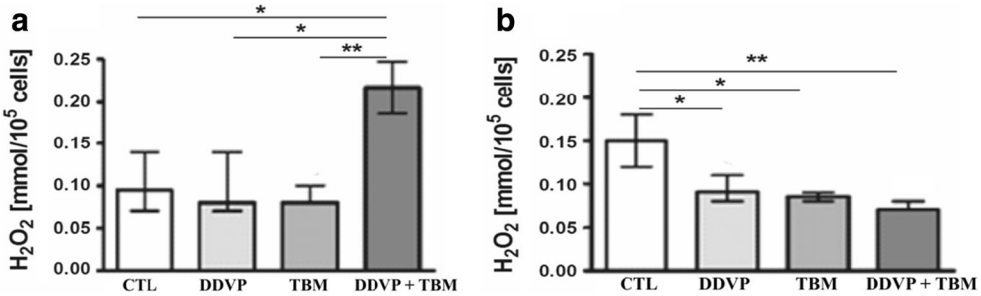

Fig. 1 Production of H_2O_2 by peritoneal adherent cells on day 7 (**a**) and day 21 (**b**) of tumor transplantation. Tumor cells (10^7/100 μl) were inoculated subcutaneously into both the TBM and DDVP-TBM groups. CTL (mice fed with basal diet); DDVP (diets containing 10 mg/kg/day of DDVP); TBM (Tumor-bearing mice fed with basal diet); DDVP + TBM (diets containing 10 mg/kg/day of DDVP in a tumor-bearing mice). Values are expressed as medians with minimum and maximum range (Mann-Whitney statistical test; $p < 0.05$; *$p < .05$; ** $p < .01$)

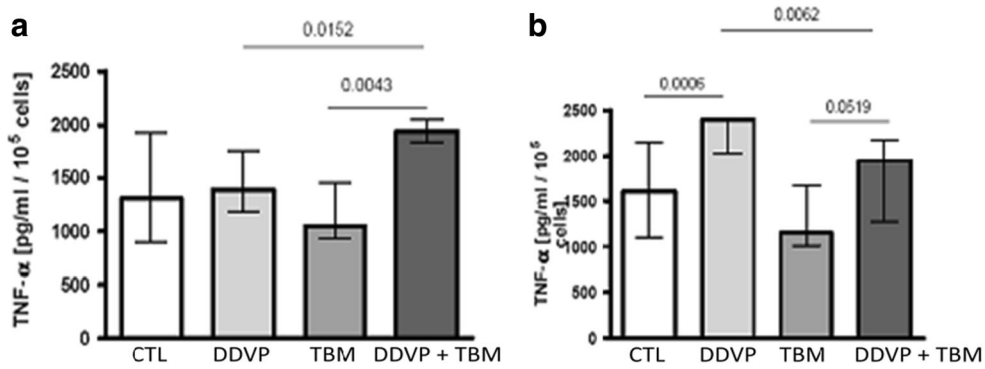

Fig. 2 Production of TNF-α by peritoneal adherent cells on day 7 (**a**) and day 21 (**b**) of tumor transplantation. Tumor cells (10^7/100 μl) were inoculated subcutaneously into both the TBM and DDVP-TBM groups. CTL (mice fed with basal diet); DDVP (diets containing 10 mg/kg/day of DDVP); TBM (Tumor-bearing mice fed with basal diet); DDVP + TBM (diets containing 10 mg/kg/day of DDVP in a tumor-bearing mice). Values are expressed as medians with minimum and maximum range (Mann-Whitney statistical test; $p < 0.05$)

structure of lymphohematopoietic organs in healthy male Wistar rats. This is probably because DDVP molecules have a high tropism for the heart, and generally, it is not found in other organs due to some enzymatic degradation (Abe et al. 2008). The OP degradation processes can also occur through enzymatic reactions in birds, fish, insects, and mammals via different kinetics, mechanisms, and transformation products. These transformed products, even with several hundred times lower IC50 (between 20 and 1090 mg/kg in animals - Abe et al. 2008) cause various diseases of the nervous and immune system (Colović et al. 2013). Studies with low doses of pesticides have gained prominence over the last several years, but the consequences of their intake are still unclear.

On the other hand, high levels of H_2O_2 and TNF release were observed in PAC culture at the beginning of tumor development (day 7 after tumor inoculation) in the DDVP-treated group. TNF production remained high until the 21st day after tumor implantation, and according to Patel and Patel (2017), this observation may be associated with mouse body weight loss and tumor weight increase in the DDVP group, showing a possible action of pesticides on the different macrophage receptors for this cytokine. This large amount of TNF induces apoptotic cell death, inflammatory responses, and can be released by activated macrophages to function as a cell signaling protein, responsible for several metabolic derangements (Argiles et al. 1998; Idriss and Naismith 2000). Podstawka (1994) demonstrated that high doses of OPs stimulate the production of mediators and promote the release of TNF, and our study demonstrated that in our experimental conditions, similar results were observed in mice exposed to lower doses of DDVP. Moreover, Hubbard (1999) showed that high levels of H_2O_2 and TNF in PACs and downregulation of H_2O_2 as the tumor development advances are a consequence of activated macrophages interacting with IFN-ɣ produced during a cell immune reaction. It demonstrates a marked increase in the expression of MHC class II molecules and strong tumoricidal activity by producing high levels of oxygen or nitrogen intermediates. TNF family members exert their biological effects through the TNFR (TNF receptors) superfamily of cell surface receptors (Baud and Karin 2001, Aggarwal 2003). TNFR1 is constitutively expressed in most cell types, and multiple experimental approaches have confirmed that TNFR1 mediates the majority of biological effects attributed to TNF (Shen and Pervaiz 2006). Its binding triggers a series of intracellular events in the JNK pathway (also known as stress-activated protein kinases), which has important functions in immunity and inflammation, and in the control of cell proliferation, differentiation, and apoptosis (Wajant

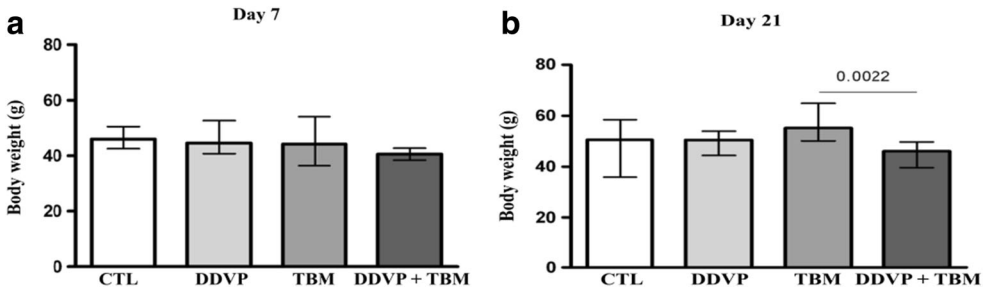

Fig. 3 Weight changes of the animals from different groups on day 7 (**a**) and day 21 (**b**) of tumor transplantation. Tumor cells (10^7/100 μl) were inoculated subcutaneously into both the TBM and DDVP-TBM groups. CTL (mice fed with basal diet); DDVP (diets containing 10 mg/kg/day of DDVP); TBM (Tumor-bearing mice fed with basal diet); DDVP + TBM (diets containing 10 mg/kg/day of DDVP in a tumor-bearing mice). Values are expressed as medians with minimum and maximum range (Mann-Whitney statistical test; $p < 0.05$)

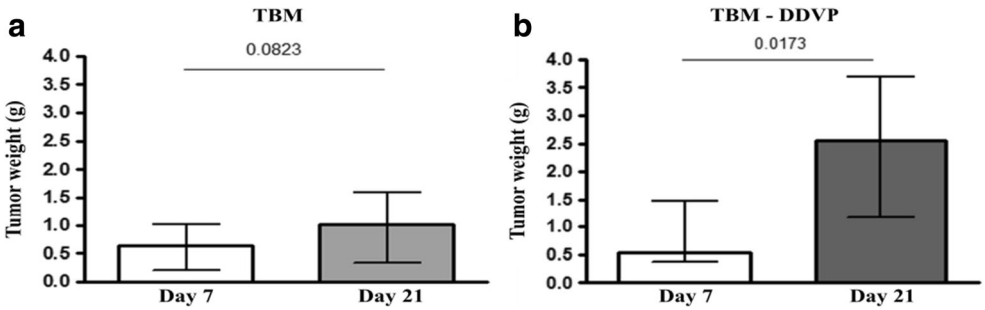

Fig. 4 Difference in tumor weight between TBM (**a**) and TBM-DDVP (**b**) groups after 7 and 21 days after tumor inoculation. Values are expressed as medians with minimum and maximum indicated. (Mann-Whitney statistical test; $p < 0.05$)

et al. 2003; Chen and Goeddel 2002), and both TNF and ROS are potent activators of JNK (Shen and Pervaiz 2006).

Moreover, on the macrophage surface, there is also a family of molecules classified as scavenger receptors, which have the ability to bind modified low-density lipoprotein (LDL), such as acetylated LDL (AcLDL) and oxidized LDL (OxLDL). They bind modified LDL or any other polyanionic ligands and immunomodulate the macrophage anti-tumor response (Plu ddemann et al. 2007). According to Proskocil (2013), low-levels of an OP compound, Parathion, activate macrophages leading to the release TNF and modulation of metabolism. Additionally, in acute and rather subchronic or chronic OP exposure, induction of oxidative stress has been reported as one of the main mechanisms of its toxicity (Ranjbar et al. 2005; Salem 2016). ROS may be generated as a result of the metabolism of OPs by cytochrome P450s (Chambers et al. 2001), changing the activity of antioxidative enzymes (catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase) and modulating oxidative stress parameters and lipid peroxidation (Colovic et al. 2010; Akhgari et al. 2003; Abdollahi et al. 2004). Considering that OP compounds can increase lipid peroxidation, in our study, we propose that oxidized phospholipids can be found in OxLDL, and these endogenous toxins can activate macrophages, thereby initiating a feed-forward mechanism in which additional inflammatory mediators and oxidants are released from the activated macrophages (Ross et al. 2014). Free cholesterol accumulation in macrophages can trigger a marked synthesis and secretion of the pro-inflammatory cytokines such as TNF (Li et al. 2005) which increases apoptosis of cells leading to a cachexic status in the mice. Furthermore, Ross et al. (2014) showed that scavenger SR-A and CD36 activity is AcLDL-dependent, and its upregulation can contribute to higher macrophage adhesion and monocyte differentiation to macrophages in a microenvironment (Huh et al. 1996) further increasing the inflammatory response. Additionally, tumor factors can depress the ability of macrophages to carry out phagocytosis and lysis (Tavares et al. 2000; Monti et al. 2004; Kuang et al. 2007). The initial ROS and TNF release initializes a cascade that activates the JNK pathway, which plays an important role in cell differentiation, apoptosis, and inflammation. High levels of TNF, a pro-inflammatory cytokine that is released, can be DDVP-dependent, acting on macrophage receptors and working toward a favorable tumor microenvironment.

Altogether, our results indicate that even at low doses, the intake of DDVP results in weight loss in mice and increases tumor mass associated with the modulation of H_2O_2 release and production of high levels of TNF. These data are important as the consumption of pesticides hinders the action of the immune response against tumors and, consequently, creates favorable conditions for the development of neoplasia. Moreover, studies that define how elements of macrophage cholesterol homeostasis are dysregulated by environmental and endogenous toxins also are very important for understanding animal and human health. This finding is important since this event contributes to the triggering of inflammation and altered immune homeostasis, and thus, may produce immunosuppressive activities.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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