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2,3,7,8-tetrachlorodibenzo-*p*-dioxin and the viral infection

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ABSTRACT

Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a widespread highly toxic environmental contaminant, suppresses immune response and leads to an increased susceptibility to infectious agents. In particular, several studies have provided evidence that TCDD decreases resistance to numerous viruses. Indeed, *in vivo* and *in vitro* investigations showed that the presence of TCDD is able to interfere with the replication of both human and animal viruses, such as influenza A viruses, coxsackie virus B3, immunodeficiency virus type-1 (HIV-1), cytomegalovirus (CMV), herpes simplex II, and bovine herpesvirus 1. Moreover, TCDD could induce an exacerbation of latent infection produced by HIV-1, CMV or Epstein-Barr virus. In this review, we first describe the general effects of TCDD exposure on mammalian cells, then we focus on its influence on the viral infections. Overall, the available data support the concept that TCDD exposure may act as an additional risk factor in promoting of viral diseases.

1. Introduction

Several studies have established that the immune system is one of the most liable targets for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a widely distributed and persistent environmental contaminant, also known as dioxin. Although cellular and molecular mechanisms of TCDD immunotoxicity are not well identified, suppressed humoral and cell-mediated immune responses, as well as decreased host resistance to infectious disease have been observed in experimental animals (Thigpen et al., 1975; Luster et al., 1979; Clark et al., 1981, 1983; House et al., 1990; Funseth and Ilbäck, 1994; Yang et al., 1994; Garssen et al., 1995; Burleson et al., 1996; Warren et al., 2000; Funseth et al., 2000, 2002; Nohara et al., 2002; Vorderstrasse et al., 2003; Kerkvliet, 1995; Mandal, 2005; Ilbäck and Friman, 2007; Fracchiolla et al., 2011; Phadnis-Moghe et al., 2016). Low-dose exposure of both humans and animals to environmental pollutants may influence the immune system and the pathogenesis of various infectious diseases. Indeed, many studies have shown that the suppression of the immune system is typically associated with an increased susceptibility and severity of infective pathologies. In particular, as reviewed by Ilbäck and Friman (2007), the environmental contaminants may influence the virulence of microorganisms and/or the susceptibility to infections among hosts. In addition, there is an emerging suggestion that maternal and early-life exposures to common environmental contaminants may have a critical impact on susceptibility to infection later in life (Nagayama et al., 2001; ten Tusscher et al., 2003; Smith et al., 2008; Leijs et al., 2009; Winans et al., 2011;). The earliest evidence describing the effects of TCDD on infectious diseases was shown by Thigpen et al. (1975), who reported that extremely low levels of TCDD exposure in mice followed by infection with *Salmonella bern* resulted in an increased mortality and a decreased time range from infection to death. Conversely, in the case of Herpesvirus suis infection (also known as pseudorabies virus) TCDD had no significant effect on mortality in the pseudorabies-infected mice. These authors concluded that the exposure to very low doses of environmental contaminants, such as TCDD, has the capacity to affect host defense. After Thigpen's paper, in the last 40 years, many research teams have described that dioxin exposure negatively affects the resistance to numerous infectious agents such as bacteria, viruses, and parasites. In this paper we focus on viruses infections (Tables 1 and 2), especially reviewing the biological effects of the cellular exposition to dioxin on the both the progression and the outcome of the infective disease.

Abbreviations: TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; AhR, Aryl hydrocarbon Receptor; 2, 4,5-T, 2,4,5-trichlorophenoxyacetic acid; NK cells, natural killer cells; CB3, human coxsackievirus B3; HIV-1, Human immunodeficiency virus-1; CMV, cytomegalovirus; HSV-II, herpes simplex virus II; MDBK cells, EBV, Epstein-Barr virus; BHV-1, bovine herpesvirus 1; MDBK cells, Madin-Darby bovine kidney cells; bICP0, BHV-1 infected cell protein 0

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Table 1
Summary of investigations showing that TCDD is able to interfere with the replication of human viruses..

Virus	*In vivo*	*In vitro*	Reference
Influenza A viruses			
A/Taiwan/1/64 (H2N2)	B6C3F1 mice	–	(House et al., 1990)
Rat-adapted influenza virus (RAIV)	Fischer 344 rats	–	(Yang et al., 1994)
A/Hong Kong/8/68 (H3N2)	B6C3F1 mice	–	(Burleson et al., 1996)
A/HKx31 (H3N2)	C57Bl/6 mice	–	(Warren et al., 2000)
A/PR/34/8 (H1N1)	B6C3F1 (C57Bl/6×C3H), BALB/c, C57Bl/6N, DBA2mice	–	(Nohara et al., 2002)
A/HKx31(H3N2)	C57Bl/6 mice	–	(Vorderstrasse et al., 2003)
Human coxsackievirus B3	A/J-mice	–	(Funseth and Ilbäck, 1994) (Funseth et al., 2000, 2002)
Human immunodeficiency virus-1 (HIV-1)	–	MT-4 cells	(Pokrovsky et al. 1991)
HIV-1	–	U1 cells	(Gollapudi et al., 1996)
HIV-1	–	OM 10.1 cells	(Ohata et al., 2003)
Herpesviruses			
Herpesvirus suis	C57BL/6Jfh (J67) mice	–	(Thigpen et al., 1975)
Herpesvirus II	C57Bl/6 mice	–	(Clark et al., 1983)
Cytomegalovirus (CMV)	TOX-Wistar rats	–	(Garssen et al., 1995)
CMV	–	MRC-5 cells	(Murayama et al., 2002)
Epstein-Barr virus (EBV)	–	COS7; MCF7 cells	(Kashuba et al., 2006)
EBV	–	B95-8; P3HR1 cells	(Inoue et al., 2012)

Table 2
Summary of investigations showing that TCDD is able to interfere with the replication of animal viruses..

Virus	*In vivo*	*In vitro*	Reference
Bovine herpesvirus 1 (BHV-1)	–	MDBK cells	(Fiorito et al., 2008a,b, 2010, 2013, 2014a, 2014b) (Santamaria et al., 2011; Fiorito and De Martino, 2014)
BHV1	Cattle	–	(Fiorito et al., 2015)

2. TCDD

TCDD is a prototype of a group of compounds named as polyhalogenated aromatic hydrocarbons. It is well established that TCDD is not intentionally generated. Indeed, it is a byproduct of some industrial processes, including chlorination of phenolic substances; however uncontrolled waste combustion actually represents the largest source of dioxin as pollutant. TCDD is persistent in the environment and bioaccumulative in living organisms. Because of its highly lipophilic nature, dioxin shows a special tropism for adipocytes tending to accumulate in the adipose fraction of body tissues and organs. Humans are generally exposed to this type of environmental toxins through the dermal absorption but mainly *via* the dietary intake. Indeed, through the food chain TCDD is incorporated into products of animal origin naturally rich in fat, such as milk, cheese, meat, and seafood, as well as in drinking water, soil, dust, smoke, and air. From the bioorganic accumulation sites, TCDD can be released slowly over the years to produce a variety of biological effects over time. Although currently other mechanisms cannot be excluded, the main molecular mechanism of action by which TCDD exerts its biochemical effects in vertebrate species is through the Aryl hydrocarbon Receptor (AhR) stimulation, a ligand-activated transcription factor belonging to the basic helix-loop-helix-PER-ARNT-SIM superfamily of proteins. In the AhR signaling pathway the activation of AhR results in its dissociation from the Hsp90/XAP2/p23 chaperone proteins complex and following dimerization with aryl hydrocarbon receptor nuclear translocator (ARNT) (Hogenesch et al., 1997; Kazlauskas et al., 2000; Mulero-Navarro and Fernandez-Salguero, 2016). The AhR/ARNT complex translocates into nucleus where it interacts with aryl hydrocarbon responsive elements (AhREs) in the promoter of various AhR-responsive genes activating their transcription (Beischlag et al., 2008). Binding of AhR/ARNT leads to several biological and toxicological effects including induction of numerous phase I and II xenobiotic-metabolizing enzymes as cytochrome P-450 isoforms, particularly CYP1A1, CYP1A2, CYP1B1, CYP2A1, and UDP-glucuronosyl transferase UGT1A6 (Zhang et al., 1998; Okino and Whitlock, 1995; Ko et al., 1996; Mandal, 2005; Amenya et al., 2016). In addition, several other genes are transcriptionally regulated by AhR activation, as cell cycle proteins, ribosyltransferases, cell adhesion proteins and others (Ma et al., 2001; Denison et al., 2011). Emerging evidence indicates that the activation of AhR influences host cell responses to viral infection through immunomodulation (Sulentic et al., 2000; Lawrence and Vorderstrasse, 2004; Vorderstrasse et al., 2004; Head and Lawrence, 2009; Boule et al., 2014; Phadnis-Moghe et al., 2016). Dioxin can provoke a wide range of tissue- and species-specific toxic effects, such as chloracne (a persistent cystic and hyperkeratotic skin condition), gastric epithelial hyperplasia, liver damage, disruption of hormone signaling pathways, reproductive and developmental defects, immunotoxicity, wasting syndrome, changes in sex ratio, and several types of cancer (Mandal, 2005; White and Birnbaum, 2009). In addition, Germolec et al. (2012) have recently reported that TCDD can promote autoimmunity following exposure during fetal or early neonatal development. For example, a single exposure to TCDD during mid gestation was shown to slightly enhance anti-DNA antibodies and/or glomerular immune complex deposits in non-autoimmune C57BL/6 or lupus-predisposed SNF1 mice. Moreover, neonatal exposure of NFS/sld mice to TCDD induced a Sjögren's syndrome-like disease along with increased anti-SS-A/Ro and anti-SS-B/La autoantibodies. As reviewed by White and Birnbaum (2009), the history of anthropogenic dioxin production and dioxin poisoning is very old and still continues now. The earliest evidence of man-made dioxin molecules comes from a chemical production plant in Germany that manufactured washing soda. Chloracne, which represents a characteristic sign of dioxin exposure, was first described in German industrial workers in 1897. In general, most reported human exposures have been the result of unintentional production or spills, as was the case for its formation as a byproduct of Agent Orange, an herbicide containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and contaminated with dioxin. Agent Orange was widely used as a defoliant in Vietnam, between 1962 and 1970, during the Vietnam war, and persistent chloracne was observed in exposed people. The American military exposure to Agent Orange was also associated with an increased risk of diabetes and of soft-tissue sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia (Michalek and Pavuk, 2008). In 1976, in Seveso (Italy), an explosion taken place at a plant producing 2,4,5-trichlorophenol, a compound developed during the synthesis of 2,4,5-T. As consequence, some weeks after the explosion, several exposed people developed skin lesions as chloracne. In the following years, studies in the exposed people provided evidence on the possible role of TCDD as a

human carcinogen and to enhance risk for *cardiovascular* diseases, diabetes, and as endocrine disruptor. In particular, studies of surveillance on Seveso people reported an excess of lymphatic and hematopoietic tissue neoplasms (Pesatori et al., 2009), an increased all-cancer mortality 15–20 years after exposure among those living in the most contaminated area (Pesatori et al., 2009; Boffetta et al., 2011), or a modified neonatal thyroid function subsequently to the first exposure (Baccarelli et al., 2008). After the Seveso accident, studies in rats showed that two-year chronic exposure to TCDD at low dose, as 0.01 μg/kg/day, induced an increased risk of hepatocellular carcinomas as well as various squamous cell carcinomas (Kociba et al., 1978, 1979; White and Birnbaum, 2009). Finally, one of the most recent episodes involved the ukrainian Prime Minister Victor Yushchenko, who was intentionally poisoned with TCCD in 2004. Before the presidential election, Yushchenko was affected first by acute pancreatitis, then by profound facial acne and edema. The excess of dioxin levels in his blood samples revealed chloracne (Saurat et al., 2012). In human, the maximum tolerable daily intake is 4 pg/kg, while Yushchenko had a single dose of 20 μg/kg. Indeed, he received a single oral dose of about 5 million-fold higher than the tolerable daily intake in human (Saurat et al., 2012). Skin lesions were hamartomas, accompanied by a complete involution of sebaceous glands (Saurat et al., 2012). Furthermore, a clinical study on the TCDD poisoning in Yushchenko reported the identification and measurement of two TCDD metabolites - 2,3,7-trichloro-8-hydroxydibenzo-p-dioxin and 1,3,7,8-tetrachloro-2-hydroxydibenzo-p-dioxin, - identified in the faeces, blood serum, and urine. The half-life of TCDD in Yushchenko was 15.4 months (Sorg et al., 2009).

Several studies, including our recent findings, demonstrate the involvement of dioxin in the genesis of tumors. Although the molecular mechanisms for carcinogenicity by dioxin have not been elucidated until now, in 1997 TCDD was classified as a cancer promoter by the International Agency for Research on Cancer (IARC, 1997). This classification is based on studies performed in laboratory animals showing that TCDD induces the formation of neoplastic lesions in the liver, lung, oral mucosa and skin. For instance in mice, exposure to TCDD stimulates the proliferation of epithelial cells within the skin tissue in a tissue-dependent manner, as well as increases proliferation of cultured cells, such as human keratinocytes (Ray and Swanson, 2009), late gestational ureteric cells (Bryant et al., 2001), human breast cells (Ahn et al., 2005), and bovine kidney cells (Fiorito et al., 2008a, 2011). By examining the tumor-promoting activities of dioxin, these findings are in accordance with a previous study indicating that epithelial cells are the most responsive to the dioxin effects (Poland et al., 1982).

3. TCDD and the human viruses

3.1. TCDD and influenza A viruses

In general, the most published research findings concern the effects of dioxin on influenza virus infections. Several kinds of environmental contaminants could contribute to the development of respiratory diseases. For example, heavy metals, like cadmium, whose sources are mainly food consumption, soil and cigarette smoke, may induce oxidative stress which directly enhances the ability of influenza virus to replicate in the host cell (Checconi et al., 2013). Respiratory infections are among the top 10 leading causes of death, and common respiratory pathogens such as influenza viruses may cause pandemic disease. Many studies have proposed that AhR activation can involve both leukocytes and non-immune cells by using influenza A virus as a model of respiratory viral infection. Thus, functional changes as suppressed lymphocyte responses and increased inflammation in the infected lung were observed. Indeed, one of the most adverse effects of TCDD is represented by a decrease in host resistance to influenza A virus (House et al., 1990; Burleson et al., 1996; Warren et al., 2000; Vorderstrasse et al., 2003; Teske et al., 2008; Head and Lawrence, 2009; Jin et al., 2010; Boule et al., 2014). House et al. (1990) described a significant dose-related suppression in induction of both IgM and IgG antibody-forming cells in adult female B6C3F1 mice after administration of a single dose of TCDD at 10, 1.0, or 0.1 μg/kg, and TCDD exposure induced an increased mortality of mice to influenza A/Taiwan/1/64 (H2N2) virus.

In Fischer 344 rats the administration of 3.0 and 10.0 μg/kg TCDD provoked a suppression of influenza virus-augmented natural killer (NK) cells activity, while the spontaneous NK activity was not affected (Yang et al., 1994). Burleson et al. (1996) showed that a single dose of TCDD at 0.10, 0.05, or 0.01 μg/kg induced an increase in mortality to influenza A/Hong Kong/8/68 (H3N2) virus when mice were challenged 7 days after TCDD administration. In addition, Vorderstrasse et al. (2003) carried out experiments in C57Bl/6 mice treated with 1, 2.5, 5, 7.5 or 10 μg/kg TCDD one day prior to influenza virus challenge. In sacrificed mice the authors evidenced that lymphocyte migration to the lung and the production of virus-specific IgG2a, IgG1, and IgG2b antibodies were significantly reduced, even at the lower doses, while IgA were significantly enhanced in all groups treated with TCDD. TCDD exposure also induced an increase in pulmonary neutrophilia in infected mice. The authors thereby have suggested that decreased antibody production and increased inflammation might contribute to the death of mice exposed to TCDD. Warren et al. (2000) reported that a single oral dose of 1–10 μg TCDD/kg caused death in mice infected with a non-lethal influenza A virus (A/HKx31). With reference to influenza A virus infection, however, these authors also showed that mortality varied widely between experiments at equivalent doses of TCDD. In this context, Nohara et al. (2002) have suggested that the apparent discrepancies in the effects of TCDD described above may be due to many factors, including combinations of TCDD levels of exposure and mouse strain used. Intriguing, in order to confirm whether TCDD at doses as low as 10 ng/kg increased the mortality of influenza A virus-infected mice as reported by Burleson et al. (1996), Nohara et al. investigated the effect of TCDD in the dose range of 0–500 ng/kg on the mortality of mice infected with influenza A type virus A/PR/34/8. They also explored the sex- and strain-dependency of host resistance in male B6C3F1 mice and in female C57Bl/6, BALB/c, and DBA/2 mice by administering the same dose range of TCDD. Their results demonstrated that TCDD doses up to 500 ng/kg did not increase the mortality of virus-infected mice in any of the strains. As consequence, these authors conclude that the increase in mortality caused by TCDD in influenza A virus infection is not caused by host resistance impairment, but to an as yet unknown mechanism (Nohara et al., 2002). We hypothesize that TCDD exposure coupled to viral infection may induce a variety of biological effects also depending by the viral subtype.

3.2. TCDD and coxsackieviruses

The coxsackieviruses belong to the enteroviruses, which are responsible for some enteroviral infections in humans; nevertheless the majority of these does not determine apparent symptoms, or at most causes simply minor illness related to the upper respiratory or gastrointestinal tract. Rarely coxsackie B viruses may provoke myocarditis, pancreatitis, or meningoencephalitis. The group of Ilbäck described that A/J-mice were infected with the human coxsackievirus B3 (CB3) and then injected, at 4 and 7 days of the infection, with [^{14}C] TCDD (about 65 μg/kg). One day after TCDD treatment, the authors detected an increased TCDD uptake in spleen, thymus, heart, pancreas, liver and brain during the CB3 infection, and this increased uptake was significantly most marked both on day 4 and 7 post inoculation (Funseth and Ilbäck, 1994). Subsequently, the same group described that A/J mice, one day before infection with CB3, were injected intraperitoneally with ^{3}H-TCDD (about 0.5 μg TCDD/kg). Then, at different days various body organs and *tissues* -including spleen,

thymus, heart, pancreas, liver, thyroid, skeletal muscle, adipose tissue, lung, kidney, adrenals, testis, epididymis, brain and blood - were collected. The authors showed that a common infection with CB3 in mice causes redistribution of a beforehand accumulated environmental pollutant, resulting in increased concentrations and increased toxicity in target organs, such as thymus and brain (Funseth et al., 2000). In addition, mice exposed to TCDD had a decreased ability to survive infection with CB3 (Funseth et al., 2002).

3.3. TCDD and human immunodeficiency virus - 1

Human immunodeficiency virus-1 (HIV-1), a cytopathic retrovirus, is the primary etiological agent of acquired immunodeficiency syndrome (AIDS). In MT-4 cell cultures (human leukemia T cells) infected by HIV-1 virus, a significant increase of virus production after *in vitro* treatment with 10–150 nM TCDD has been showed by Pokrovsky et al. (1991). Gollapudi et al. (1996) reported that dioxin (10–200 nM) triggers HIV-1 gene expression, causing an increased production of HIV in chronically infected promonocytic U1 cells. This dioxin effect seems to be mediated, at least partially, by activation of nuclear factor kappa-B, a key cellular transcription factor that regulates HIV-replication playing a key role in the induction of both HIV and cytokine genes. In addition, TCDD stimulated the production of tumor necrosis-α in U1 cells. Therefore the authors have suggested molecular alterations for increased viral replication in cells exposed to dioxin (Gollapudi et al., 1996). Furthermore, Ohata et al. (2003) indicated that TCDD (10 nM) activates HIV-1 replication in promyelocytic OM 10.1 cell line, latently infected with HIV-1. The authors concluded that HIV-1 infected individuals chronic exposure to polyhalogenated aromatic hydrocarbons, such as TCDD, may contribute to the clinical development of AIDS.

3.4. TCDD and herpesviruses

As reported above, Thigpen et al. (1975) argued that oral doses of 1–20 μg TCDD/kg per week for 4 weeks had no effect on the mortality of mice infected with Herpesvirus suis. Conversely, studies with herpesvirus II (HSV-II), indicate an increased mortality by TCDD intraperitoneally injected in mice once a week for 4 weeks at doses of 0.04, 0.4, or 4.0 μg/kg (total dose of 0.16, 1.6, and 16.0 μg/kg) (Clark et al., 1983).

Cytomegalovirus (CMV) is an ubiquitous herpesvirus contracted by 50–90% of normal adults, depending on geographic location. In particular, CMV infects most individuals early in life and establishes thereafter a lifelong latent infection characterized by the persistence of viral genome without the production of infectious virions. Latently infected CMV is frequently activated in immunocompromised individuals. Garssen et al. (1995) showed that viral titers in the salivary glands of rats infected with CMV are elevated by dioxin exposure *in vivo*. Treatment of MRC-5 cells, a human embryonic fibroblast cell line, with 0.0001 pg/ml TCDD increased the cytopathic effects on CMV-infected cultures and the cytomegalovirus replication with a concomitant increase in CMV UL54 DNA levels. Moreover, CMV-infected MRC-5 cells increased gene *expression via AhR stimulation*. These results suggest that TCDD may contribute both to the development of opportunistic diseases by reactivation of latent CMV infection and to the regulation of CMV replication through the AhR influence (Murayama et al., 2002).

Epstein-Barr virus (EBV) is an ubiquitous herpesvirus that infects more than 90% of the world's population. Generally, the infection is asymptomatic and the virus establishes latently in resting recirculating memory B cells (Babcock et al., 1998). B cells are a main component of humoral immunity and represent a sensitive target for TCDD through an induction of AhR gene and protein expression (Sulentic et al., 1998; Suh et al., 2002; Sulentic and Kaminski, 2011; Phadnis-Moghe et al., 2016). Moreover, several studies demonstrated that AhR interacts directly with viral proteins and affects viral latency. In fact, it has been observed that the EBNA-3, an EBV-encoded nuclear antigens required for immunoblastic transformation and continuous proliferation of B-cells, interacts specifically with AhR (Kashuba et al., 2006). Following activation of the AhR, EBNA-3 is able to counteract the inhibitory effect of TCDD on the growth of EBV-carrying lymphoblasts (Kashuba et al., 2006). Inoue et al. (2012) evaluated the possibility that ligand-activated AhR reactivates EBV. The induction of lytic cycle produces new viral infection and EBV-associated cellular transformation, and this induction could represent a risk factor for both malignant transformation and the development of autoimmune diseases, such as Sjögren's syndrome. Those studies were performed on saliva samples collected from patients with primary Sjögren's syndrome, from healthy controls and patients with severe dry mouth. TCDD (1–100 nM) enhanced the EBV BZLF1 gene transcription, which mediates the switch from the latent to the lytic form of EBV infection in EBV-positive B cell lines and in a salivary gland epithelial cell line. In addition, TCDD-induced increases in BZLF1 mRNA and EBV genomic DNA levels in the B cell lines. The authors conclude that AhR ligands, such as TCDD, are able to induce the EBV reactivation in activated B cells and salivary epithelial cells, and these ligands are involved in Sjögren's syndrome. Jointly these findings may account for the immunological disturbances and exacerbation of latent EBV infections frequently observed during the prolonged exposure to xenobiotics (Stancek et al., 1995).

4. Dioxin and the animal viruses

Over the past decade, high levels of TCDD have been detected in dairy products from some areas of Campania Region (Italy) (Diletti et al., 2003; Santelli et al., 2006; Esposito et al., 2009, 2010) where bovine herpesvirus 1 (BHV-1) is widespread (2004/558/EC, 2004; Ackermann and Engels, 2006). BHV-1, one of the most important viral pathogen of cattle, has been studied by the Section of Infectious Diseases at the Department of Veterinary Medicine and Animal Production (University of Naples Federico II, Naples, Italy) for over 30 years (Martone et al., 1981; De Martino et al., 2003a, 2003b, 2007). Thus, during “dioxins crisis”, we started to study the effect of TCDD on BHV-1, an animal virus. As a member of the alpha-herpesvirinae subfamily, BHV-1 is an important pathogen responsible for infectious bovine rhinotracheitis (IBR), infectious pustular vulvovaginitis (IPV), conjunctivitis, abortions as well as shipping fever, a complicated infection of the upper respiratory tract. Moreover, BHV-1 may induce immunosuppression, thus rendering cattle more susceptible to secondary bacterial infections, and leading to pneumonia and occasionally to death (Tikoo et al., 1995; Jones, 2003). In Madin-Darby Bovine Kidney (MDBK) cell line, an epithelial-like bovine cell line commonly used for growing and assaying BHV-1 (Shrivastava and Le Jan, 1982; De Martino et al., 2003a, 2003b), our research group has detected the presence of AhR (Fiorito et al., 2014a). In this *in vitro* experimental model, we have demonstrated that TCDD induces significant cell proliferation (Fiorito et al., 2008a) and also impairs cellular iron homeostasis, leading ultimately to important changes in the intracellular labile iron pool extent (Santamaria et al., 2011). In line with many recent reports, cell growth modifications coupled to iron homeostasis impairment could be associated to the neoplastic transformation of the bovine cells and to cancer development (Toyokuni, 2009; Fiorito et al., 2011; Fiorito and De Martino, 2014). Analysis of MDBK cultured monolayers morphology revealed some death alterations in a large number of exposed cells, without however apoptosis and/or necrosis hallmarks; we rather found that dioxin activated cell death by autophagy (Fiorito et al., 2008a; Fiorito et al., 2011). Hence, dioxin initiates divergent pathways of cell proliferation and autophagic cell death in an epithelial kidney cell line. In this way our data establish the requirement for autophagy in the maintenance of MDBK cells exposed to dioxin, providing that autophagy protects against proliferative

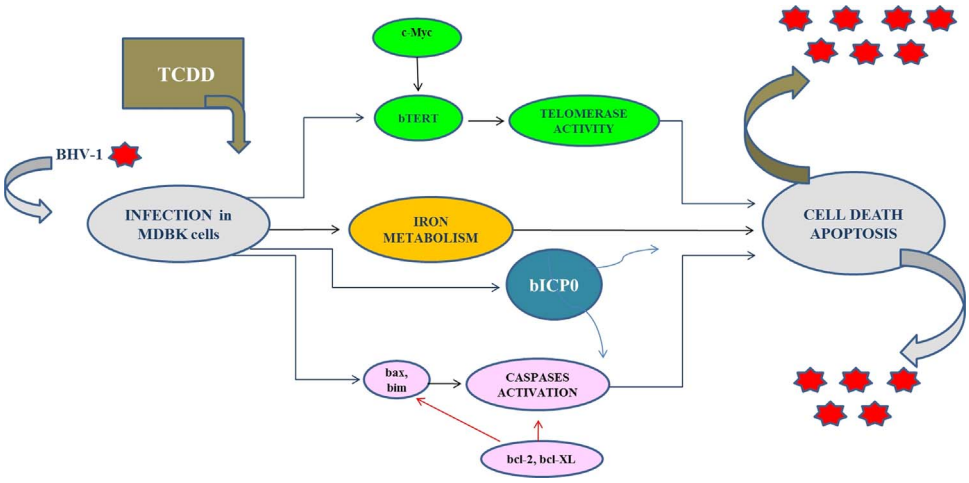

Fig. 1. Schematic diagram illustrating the hypothesized mechanisms as to how TCDD exerts its effects on the BHV-1 replication, resulting in anticipated apoptotic cell death and increased virus replication.

effects induced by non-genotoxic compounds such as TCDD. Indeed autophagy serves as a protective mechanism, though persistent activation of autophagy can result in cell death, mainly following exposure to toxic agents (Fiorito and De Martino, 2014). In the same bovine kidney cells infected with BHV-1 (Cooper strain) and concurrently exposed to different TCDD concentrations (0.01, 1 and 100 pg/ml), we showed that dioxin significantly enhances BHV-1 replication in a concentration-dependent manner, increasing both cytophatic effect and viral titer (Fiorito et al., 2008a; Fiorito et al., 2014b). Moreover, during BHV-1 infection, the expression of AhR was not influenced by viral infection, whereas TCDD induced a significant AhR overexpression (Fiorito et al., 2014a).

It is known that BHV-1 induces apoptosis which occurred only during the late stages of infection (Devireddy and Jones, 1999; Geiser et al., 2008; Fiorito et al., 2008b). The presence of TCDD anticipates BHV-1-induced apoptosis by accelerating the activation of initiator caspases 8 and 9, and of executioner caspase 3, through modulation of the Bcl-2 family members (Fiorito et al., 2008b). Therefore our data provide evidence that in the presence TCDD BHV-1 induces high levels of apoptosis in MDBK cells throughout the early stages of infection. Although epithelial cells are more resistant to apoptosis (Wesselborg et al., 1993), our findings show a significant rate of apoptosis by now in the early stages of infection, suggesting that the concomitant cell exposure to TCDD may enhance apoptosis (Fiorito et al., 2008b).

More on this topic, in a previous paper our group showed that, during the early stages of infection in MDBK cells, BHV-1 significantly up-regulates telomerase activity, through a involvement of an immediate-early viral gene (Pagnini et al., 2006). While, during the late phases of infection, when BHV-1-induced apoptosis takes place (Devireddy and Jones, 1999; Fiorito et al., 2008b), we observed a down-regulation of telomerase activity (Fiorito et al., 2014a). Telomerase is a ribonucleoproteic enzyme complex which consists of an essential RNA component and a catalytic protein subunit containing the telomerase reverse transcriptase activity. Human telomerase reverse transcriptase (hTERT) catalytic subunit is a protein up-regulated by c-Myc (Wu et al., 1999). Following BHV-1 infection in MDBK cells, we found that TCDD may act as a strong inhibitor of telomerase activity (Fiorito et al., 2014a). In fact, TCDD considerably and significantly induced a down-regulation of telomerase activity, when anticipated virus-induced apoptosis occurred, by using the same experimental conditions (Fiorito et al., 2008b, 2014a). These results were observed along with reduced levels of bovine TERT (bTERT) and of c-Myc in BHV-1 infected cells in the presence of dioxin (Fiorito et al., 2014a).

Gene expression of BHV-1 is temporally expressed in three different phases identified as immediate-early (IE), early (E), and late (L), and tissue-specific factors may mediate latency and/or pathogenesis by influencing viral gene expression (Jones, 2003). Immediate-early BHV-1 infected cell protein 0 (bICP0), the bovine homologue of HSV-1 ICP0, controls the three phases of BHV-1 replication, by playing a role of strong activator or repressor of specific viral promoters (Wirth et al., 1991; Jones et al., 2006). During BHV-1 infection in bovine kidney cells, TCDD induced an increase of expression levels of both bICP0 gene and protein, as well as an anticipation of bICP0 in the cytoplasm (Fiorito et al., 2011). Consequently, we suppose that the accelerated down-regulation of telomerase activity may be the result of a correlation between bICP0 and dioxin. In fact, Pagnini et al. (2006) also observed that an immediate-early viral gene mediated the modulation of telomerase activity produced by BHV-1 (Fiorito et al., 2014a).

Still with reference to animal viruses and according with literature, DNA viruses such as BHV-1 require an iron-replete cell host to efficiently reproduce; iron bioavailability become thereby a crucial factor for viral cycle as well as for viral DNA replication (Lamarche et al., 1996; Maffettone et al., 2008; Rashed, 2011). In particular, we have provided evidence that TCDD impairs cellular iron homeostasis in mammalian cells by modulating the expression of the main cellular proteins involved in iron metabolism, leading ultimately to important changes in the extent of the labile iron pool (Santamaria et al., 2011). Taking into account that TCDD enhances the BHV-1 replication, we have also explored the effects of TCDD on iron metabolism during BHV-1 infection in MDBK cells, finding that they cause a divergent modulation of Iron Regulatory Proteins RNA-binding activity with an up-regulation of transferrin receptor 1 and a concomitant down-regulation of ferritin. This situation leads to an increase in intracellular iron content that might promote the onset of BHV-1 infection and render bovine cells even more susceptible to viral infection (Fiorito et al., 2013).

Overall, these findings suggest that TCDD exposure may act as an additional risk factor for the progression of BHV-1 infection in mammalian cells (See Diagram in Fig. 1 – Table 2). Finally, as reported above, to monitor PCDD/Fs levels in cow's and buffalo's milk from farms an extraordinary plan of official control was carried out in 2008 in Campania region. The most part of the non-compliant farms were individuate in a restricted area of region by geo-referencing analysis (Esposito et al., 2009, 2010). In the same period, to verify the possibilities of the use of data obtained *in vitro* to *in vivo* conditions, in those farms where PCDD/Fs monitoring was carried out (Esposito et al., 2009, 2010), we have performed an epidemiological analysis on the distribution of BHV-1 in cattle (Fiorito et al., 2015). To detect antibodies for IBR from cattle raised on those farms, serum and plasma

samples were collected. By using IBR-gB and IBR-gE E.L.I.S.A. kit, which represents the test procedure of choice in many European IBR programs, we have revealed a significant prevalence of IBR on samples collected from farms in contaminated areas, compared to samples collected in uncontaminated areas. Hence, TCDD may influence BHV-1 infection, promoting a significant prevalence of IBR in cattle (Fiorito et al., 2015). Moreover, we hypothesize that dioxin may also act as additional risk factor for progression of IBR in cattle, provoking animal diseases and economic losses to the cattle industry.

5. Conclusion

TCDD is a widespread, persistent, and highly toxic environmental pollutant. By acting in an orchestrated manner, dioxin can suppress immune response thereby leading to an increased susceptibility to infectious agents. Throughout this review is highlighted how the presence of dioxin is able to modify the replication of several viruses. Thus, TCDD-mediated AhR activation can act on host cell responses to influenza A viruses through immunomodulation. More, dioxin enhances viral replication, precisely in CB3, HIV-1, CMV, HSV-II, or in BHV-1 infections. In this context, AhR may interact directly with viral proteins and affect viral latency, as observed in EBV, HIV, CMV infections following exposure to xenobiotics, such as TCDD. In addition, TCDD significantly reduces telomerase activity when anticipated BHV-1-induced apoptosis occurred, as well as by interfering with iron homeostasis increases the free intracellular iron availability thereby promoting the onset of BHV-1 infection in bovine cells. Furthermore, TCDD influences BHV-1 infection, promoting a significant prevalence of IBR in contaminated cattle. Hence, the activation of AhR by TCDD can be associated with decreased host response and reduced survival *in vivo*, and with the onset of viral infections *in vitro*. On the whole, the available data support the concept that TCDD exposure may act as a risk factor for the progression of viral diseases. However, further studies are required to better characterize the biological effects of dioxin on viral diseases in humans as well as in animals.

Conflict of interest

None.

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