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Editorial

Influence of 2,3,7,8-Tetrachlorodibenzo-P-Dioxin on Bovine Herpesvirus 1 Replication

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2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most potent member of the dioxin group of chemicals, herein called dioxin, is a toxic and persistent environmental contaminant. Humans and animals are generally exposed to dioxin which is incorporated in food, mainly in products of animal origin rich in fat, but also in drinking water, soil, dust, smoke and air [1]. TCDD exerts most of its biochemical effects by binding to the Aryl hydrocarbon Receptor (AhR). AhR forms a complex with the AhR nuclear translocator (ARNT) protein by interactions with dioxin responsive elements and activates the expression of a battery of genes that catalyzes the metabolism and conjugation of xenobiotics. Thus dioxin causes a broad range of effects, including chloracne, hepatotoxicity, and reproductive toxicity, disruption of endocrine pathways, teratogenesis and thymic atrophy both in human and in experimental animals. In 1997, the International Agency for Research on Cancer has classified TCDD as a carcinogen.

Furthermore, dioxin induces immunosuppression and increased susceptibility to infectious agents [1]. For example, TCDD enhances mortality in mice infected with herpesvirus II [2], or with different subtypes of influenza A viruses [3]. Also it increases virus replication in cells infected with human immunodeficiency virus-1 [4] or cytomegalovirus [5].

In recent years, high levels of TCDD have been detected in dairy products from certain areas in the Campania Region of Italy, where Bovine herpesvirus 1 (BHV-1) is widespread. This suggested us to undertake pioneering investigations on the effects of TCDD on an animal virus, BHV-1, which is an important cattle pathogen. BHV-1 provokes upper respiratory tract disorders, genital infections and abortions. In addition, it also induces immunosuppression which can lead to secondary bacterial infections and pneumonia. Thus, BHV-1 infection causes substantial economic loss in the cattle industry [6].

We have explored the effects of dioxin on BHV-1 using Madin-Darby bovine kidney (MDBK) cells, an epithelial cell line used for growing and assaying the virus, BHV-1 (Cooper strain), in the presence or absence of different low doses of TCDD. We first studied the effect of dioxin on cells and observed that TCDD induces proliferation as well as death in some MDBK cells, though no signs of necrosis or apoptosis were observed. But we found that dioxin activates cell death with autophagy. In general, the regulated lysosomal degradation pathway of autophagy prevents cellular damage, while autophagic cell death is rarely the mechanism by which cells die [7]. Therefore our results provided the seminal data to support the concept that, in MDBK, cell death with autophagy protects against proliferative effects induced by toxic agents such as TCDD [8,9]. Whereas, following BHV-1 infection in MDBK, in the presence of different concentrations of TCDD, we observed that dioxin enhances cytotoxicity and viral replication through a dose-dependent augmentation both in cytopathy and in viral titer [8]. During BHV-1 infection, necrosis represents the predominant type of cell death in MDBK cells, while apoptosis occurred only towards the end of the productive infection, by the activation of caspases [10]. Whereas TCDD treatment anticipates BHV-1-induced apoptosis, by accelerating the activation of both initiator and executioner caspases, through the members of Bcl-2 family [11]. It is known that apoptosis can be regulated by the activity of telomerase, the enzyme responsible for telomere elongation which catalyzes the synthesis and extension of telomeric DNA repeats. So it compensates for telomere shortening during DNA replication and thus stabilizes telomeric length. It is known that several viruses can induce both up- or down-regulation of telomerase

activity. We have previously detected that BHV-1 up-regulates telomerase activity at early stages of infection [12]. While evaluating the influence of dioxin on telomerase activity during infection, we found that BHV-1 induced a significant down-regulation during virus induced apoptosis [13].

DNA viruses, such as BHV-1, are strictly dependent on iron for their proliferation as a result of the essential role that iron plays in the catalytic centre of ribonucleotide reductase, so that iron bio-availability is an important component of viral virulence. Our analysis of the effects of TCDD on iron metabolism during BHV-1 infection indicated an expansion of intracellular iron availability, which might promote the onset of BHV-1 infection and render bovine cells more vulnerable to the virus [14].

Finally, we demonstrated the presence of AhR in MDBK cells in which the expression of AhR was not influenced by BHV-1 infection. Following BHV-1 infection, TCDD induced a significant overexpression of AhR, in a dose-dependent manner [13].

Taken together, available data indicate that TCDD may act as an additional risk factor for progression of BHV-1 infection in cattle. Since very low doses of TCDD are sufficient to cause the damage herein showed, we suggest that this risk should be given adequate consideration in the care of farm animal health.

References

1. Mandal PK. Dioxin: a review of its environmental effects and its aryl hydrocarbon receptor biology. J. Comp. Physiol B. 2005, 175: 221-230.

2. Clark DA, Sweeney G, Safe S, Hancock E, Kilburn DG, Gauldie J. Cellular and genetic basis for suppression of cytotoxic T cell generation by haloaromatic hydrocarbons. Immunopharmacology. 1983, 6: 143-153.

3. Head JL, Lawrence BP. The aryl hydrocarbon receptor is a modulator of anti-viral immunity. Biochem. Pharmacol. 2009, 77: 642-653.

4. Gollapudi S, Kim CH, Patel A, Sindhu R, Gupta S. Dioxin activates human immunodeficiency virus-1 expression in chronically infected promonocytic U1 cells by enhancing NF-kappa B activity and production of tumor necrosis factor-alpha. Biochem. Biophys. Res. Commun. 1996, 226: 889-894.

5. Murayama T, Inoue M, Nomura T, Mori S, Eizuru Y. 2,3,7,8-tetrachlorodibenzo-p-dioxin is a possible activator of human cytomegalovirus replication in a human fibroblast cell line. Biochem. Biophys. Res. Commun. 2002, 296: 651-656.

6. Jones C. Herpes simplex virus type-1 and bovine herpesvirus-1 latency. Clin. Microbiol. Rev. 2003, 16: 79-95.

7. Kroemer G, Levine B. Autophagic cell death: the story of a misnomer. Nat. Rev. Mol. Cell. Biol. 2008, 9: 1004-1010.

8. Fiorito F, Pagnini U, De Martino L, Montagnaro S, Ciarcia R, Florio S, Pacilio M, Fucito A, Rossi A, Iovane G, Giordano A. 2,3,7,8-tetrachlorodibenzo-p-dioxin increases bovine herpesvirus type-1 (BHV-1) replication in madin-darby bovine kidney (MDBK) cells in vitro. J. Cell. Biochem. 2008, 103: 221-233.

9. Fiorito F, Ciarcia R, Granato GE, Marfe G, Iovane V, Florio S, De Martino L, Pagnini U. 2,3,7,8-Tetrachlorodibenzo-p-dioxin induced autophagy in a bovine kidney cell line. Toxicology 2011, 290: 258-270.

10. Devireddy LR, Jones C. Activation of caspases and p53 by bovine herpesvirus 1 infection results in programmed cell death and efficient virus release. J. Virol. 1999, 73: 3778-3788.

11. Fiorito F, Marfè G, De Blasio E, Granato GE, Tafani M, De Martino L, Montagnaro S, Florio S, Pagnini U. 2,3,7,8-tetrachlorodibenzo-p-dioxin regulates bovine herpesvirus type 1 induced apoptosis by modulating Bcl-2 family members. Apoptosis 2008, 13: 1243-1252.

12. Pagnini U, De Martino L, Montagnaro S, Diodato A, Longo M, Pacelli F, Pisanelli G, Iovane G. Bovine herpesvirus type 1 (BHV-1) up-regulates telomerase activity in MDBK cells. Vet. Microbiol. 2006, 113: 231-236.

13. Fiorito F, Cantiello A, Granato GE, Marfè G, Ciarcia R, Florio S, Pagnini U, De Martino L, Iovane G. Modulation of telomerase activity, bTERT and c-Myc induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin during Bovine Herpesvirus 1 infection in MDBK cells. Toxicol. In Vitro. 2014, 28: 24-30.

14. Fiorito F, Irace C, Di Pascale A, Colonna A, Iovane G, Pagnini U, Santamaria R, De Martino L. 2,3,7,8-Tetrachlorodibenzo-p-dioxin promotes BHV-1 infection in mammalian cells by interfering with iron homeostasis regulation. PLoS One. 2013, 8: e58845.