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Reactivation of CMV and HSV-1 Among Severe COVID-19 Patients May Be Triggered by Increased Level of Pulmonary Dioxin

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Purpose: Reactivation of cytomegalovirus (CMV) infection was recently found to influence worse clinical outcome following SARS-CoV-2 infection (doi:10.1186/s13054-020-00185-x). Other findings showed that CMV and herpes simplex virus 1 (HSV-1) reactivations are observed in patients with COVID-19 acute respiratory distress syndrome (ARDS) (HYPERLINK "https://doi.org/10.1186/s13054-020-03252-3" doi:10.1186/s13054-020-03252-3). Addressing occurrence of Herpesviridae reactivation in immunocompetent patients and still unspecified triggers of reactivation, we tested potent xenobiotic 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which current body burden (DBB) ranges from 20 pg/g (TEQ in fat) in general population to 100 pg/g in older people.

Methods & Materials: In silico quantitation of active dioxin response enhancers (DRE) in promoters of viral genes. Plaque assay of viral titer. Virus DNA hybridization assay. Clinico-epidemiological analysis.

Results: In silico analysis revealed in regulatory region of CMV IE genes from 5 to 10 DRE, and from 6 to 8 DRE in regulatory region of HSV-1 IE genes. We established that a picomolar TCDD can trigger up-regulation of CMV and HSV-1 genes via AhR:Arnt transcription factor in macrophage (doi.org/10.1016/j.ijid.2012.05.265) and glial human cell lines (doi.org/10.1016/j.jalz.2016.06.1268), respectively. In fact, viral reactivation may be triggered in COVID-19 ARDS patients by higher pulmonary TCDD concentrations, as lipid storm within lungs of severe COVID-19 patients has been recently reported (doi.org/10.1101/2020.12.04.20242115). Due to hydrophobic character (Log PO/W: 7.05), TCDD partitions into inflammatory lipids in lung tissue thus augmenting its local concentration. Population-based epidemiological data on SARS-CoV-2 first wave of pandemic showed that picomolar TCDD can reactivate CMV (measured by high CMV seropositivity), as cumulative mortality rate 4.5 times was revealed in Lombardi region of Italy where after Seveso industrial accident TCDD plasma level in pre-exposed subjects still is 15 times the level in rest of Italy (doi.org/10.3389/fpubh.2020.620416). Also, Arctic Native (AN) peoples have TCDD body burden 7 times that in general population, as they consume dioxin-contaminated fat in seafood, and their COVID-19 mortality is 2.2 times of that among non-AN Alaskans (doi:10.15585/mmmr.mm6949a3).

Conclusion: TCDD in picomolar range may trigger CMV expres- sion in lung cells and commit virus to the lytic cycle, which can be applied to reactivation of Herpesviridae infection in immunocompe- tent patients with COVID-19 ARDS syndrome.

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