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Human viruses: A novel target for bHLH/PAS dioxin receptor Arnt transcription factor

Objective: The concept emerged from our findings indicated transactivation of the HIV-1 and hepatitis B virus (HBV) in human cells by 30-150 ppt 2,3,7,8-TCDD (dioxin), a potent carcinogenic xenobiotic with extremely long serum half-life in humans. Up-regulation of *Cytomegalovirus* (HCMV) in human cells was shown using 10 ppq dioxin, a level much lower than current background level in the general population (~4 ppt). Eventually, human viruses were suggested novel target genes of cellular dioxin receptor (AhR/Arnt) complex. This complex had been primarily shown binding to dioxin-responsive elements (DRE) within numerous mammalian target genes and the effect of number of DRE on dioxin gene regulating activity was established. Here, going along with the above experimental data, potentially active DRE were detected and quantified in regulatory area of several cancer-related human viruses.

Methods: Productions of infectious HIV-1 in MT4 cells, HCMV in THP-1 cells and HBV in HepG2 cells were determined using plaque assay. Viral DNAs were determined by hybridization and PCR. A computational search for DRE in viral genes was performed by SITECON, a powerful tool for detecting conservative conformational and physicochemical properties in transcription factor binding site alignments and for site recognition. Earlier SITECON efficiently detected all proved functional DREs in human *CYP1A1* and *CYP1B1*, as well as DRE in human genes encoding AhR and proteins of its cytosolic and nuclear complexes.

Results: A total of 13 bona fide DRE, all including the substitution intolerant core sequence (5'-GCGTG-3') and SITECON-selected adjacent variable sequences were used here to detect the above properties for the DRE site and conformational similarity score threshold of 0.95 was utilized to rank identified DRE. Eventually, for HCMV it was found that regulatory region of the genes encoding IE gp/UL37 has 5 DRE, 1.65 kb/UL36-6 DRE, pp65-7 DRE, pp71-7 DRE and pp150-10 DRE. Contrarily to that, each gene of different HBV proteins, as well as HIV-1 LTR, has a single promoter DRE. If juxtapose DRE numbers with experimental results, then the most susceptible candidate virus to be augmented with body burden dioxin is that one possessing at least similar to HCMV number of DRE. To this end, SITECON recognized that several known cancer associated human viruses possess multiple DREs in their promoters. Thus two Epstein-Barr virus (EBV) promoters, L1A and L1, each contain 16 DRE, and gene of EBV R1 145K has 11 DRE. Also, genes encoding some major proteins of herpes simplex virus (HSV) type 1 have from 7 to 8 promoters DRE.

Conclusion: The above support the concept and provide evidence that sub-nanomolar dioxin is able to activate DRE containing viruses. Mechanistic data obtained allow searching for inhibitors of viremia and virally driven malignancies among antagonist ligands of cytosolic AhR and modifiers of AhR/Arnt complex binding to viral DRE.

Biography

I B Tsyrlov is currently working as a CSO at XENOTOX Inc, USA since 2005. He has completed his MD (1970), PhD in Biochemistry (1973) and DSc in Molecular Toxicology (1983). He has worked as Group Leader, Head of the Laboratory, Department Chair at Russian Academy of Science, Russia and in the United States as Senior Scientist at NCI, NIH, Visiting Professor at Mount Sinai School of Medicine. He is the author of 5 monographs and 250+ peer reviewed publications.

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