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Inhibitor of DNA-Binding/Differentiation Proteins and Environmental Toxicants: Genomic Impact on the Onset of Depressive Dysfunction

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Abstract:
The ongoing growth of international occurrence of depression and its ability to co-occur with other serious medical disorders such as heart disease, cancer, diabetes, and Parkinson's disease is a current public health problem. Inhibitor of DNA-Binding/Differentiation (ID) proteins are part of a group of transcriptional factors that have been seen to be involved in neurocognitive disorders and therefore, may have influence on depressive disorders. Previously, it has been established that environmental estrogenic endocrine disruptors (EEDs) such as polychlorinated biphenyls (PCBs) & bisphenol A (BPA) have played an important role in the impact of depressive disorders. Hence, based on many studies, we consider the impact of these environmental pollutants on the group of ID proteins. Improved understanding of how the interaction of ID proteins by EED exposure can influence depressive disorders will contribute essential evidence that can further benefit our public health community with innovative knowledge to prevent these types of mental illnesses.

Keywords: depression; estrogenic endocrine disruptor; environmental factor; inhibitor of differentiation; mental disorder

1. Introduction

Depression, is a shared but serious mood disorder. It can cause severe symptoms that affect how you think, feel, and handle daily activities such as working, eating, or sleeping. Depression is one of the most common mental disorders in the United States [1-2]. An estimated 16.2 million adults in the United States have at minimum one depressive episode, which signifies 6.7% of all U.S. adults. Furthermore, depressive episodes are greater among adult females (8.5%) when compared to males (4.8%) [1-2]. Depression can occur at any age but often starts in adulthood. There are numerous forms of depression and may cultivate under distinctive conditions such as persistent depressive disorder, psychotic depression, postpartum depression, bipolar disorder, and seasonal affective disorder [1-2]. Today, there are many factors that can onset the development of depression. Currently, there is a prerequisite to identify how environmental pollutants such as estrogenic endocrine disruptors (EEDs) contribute to depressive disorder predisposition.

Estrogen, which belongs to a group of hormones, has been previously demonstrated to have numerous purposes including regulation of endocrine development and growth alongside metabolism [3]. Additionally, estrogen has been seen to affect depressive outcomes [4-6]. Because of this, depression may be predisposed to EED exposure. These categories of pollutants have the capability to alter hormone production or function. The group includes phytoestrogens, heavy metals and anthropogenic chemicals such as polychlorinated biphenyls (PCBs), bisphenol A (BPA), arsenic, phthalates, and DES (Diethylstilbestrol) [7-11]. Data has demonstrated links between EED exposure and depression [12-17]. Based on findings that demonstrate a family of transcriptional proteins, Inhibitor of DNA-Binding/Differentiation or ID proteins has been connected with depression [18-22], we will also highlight how exposure to environmental EEDs may potentiate depression outcomes via ID proteins. Overall, the goal of this review is to make links between ID proteins to EED interactions thus leading to altered results in depression. Additional research in these competences may reveal novel or more valuable modalities and aid to deliver methodologies for prevention of this disorder.

1. Inhibitor of DNA Binding/Differentiation

1.1 Background

ID proteins consist of four genes (ID1, ID2, ID3, ID4) that make up a group of transcriptional regulators. The ID family shares a widespread amino acid sequencing homology within their helix-loop-helix (HLH) domain [23-24]. ID proteins act as transcriptional regulators by dimerizing with basic HLH transcription factors such as E12, E47, and HEB [25-26]. Furthermore, they are involved in the modulation of various biological processes such as cell cycle control, angiogenesis or apoptosis, cell differentiation and proliferation, metastasis, and senescence [27-28]. ID proteins play an essential role in nervous tissue biology and remain constant through the nervous tissue development [29-31]. Depression may co-exist with other neurocognitive disorders where nervous tissue development is an important factor such as Parkinson's disease, dementia, and Alzheimer's [32-33]. Reactive oxygen species (ROS) has demonstrated to induce ID protein-facilitated dysregulation and cell proliferation in both in vivo and in vitro settings [34-36]. Additionally, it was shown by Das et al that exposure of 17-β estradiol (E2) with estrogenic endocrine disruptors (EEDs) such as polychlorinated biphenyl 153 (PCB153) to vascular endothelial cells (ECs) proliferate ROS [37]. Since ID proteins such as *ID3* are redox-sensitive, it acts as an essential factor of the ROS-stimulated proliferation of ECs and E2 to PCB153 [37-39]. Depression, which is categorized as a mood disorder is triggered when neurotransmitters, that are chemical messengers that help the brain communicate with parts of the body, are out of equilibrium. Low levels of neurotransmitters may play a role in why some individuals are more predisposed to depression including dopamine, norepinephrine, & serotonin [1]. It has been shown that these neurotransmitters have been interconnected with various levels of ROS [40-43]. As levels of ROS increase, human tissue becomes affected at a molecular level over duration of time. Since ID proteins are demonstrated to be

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redox sensitive, we predict environmental toxicants such as EEDs may enhance ROS-stimulated levels of ID proteins, thus causing the onset of depressive dysfunction.

1.2 Inhibitor of DNA Binding/Differentiation and Depressive Disorders

There has been evidence demonstrating the role of ID proteins in depressive disorders. Disruptions in behavioral and circadian rhythm-connected physiological processes are regularly seen in depressed patients. Nonetheless, contribution of the circadian system in depressive pathophysiology is incompletely comprehended. Savalli et al demonstrated that stress-stimulated anhendonic behavior in mice is connected with agitated diurnal oscillation of expression of genes: Rev-erbα, *ROR-β*, *ROR-γ*, *CRY2*, *PER1*, *CLOCK*, and *ID2* in the mouse basolateral amygdala. The aberrant control of diurnal rhythmicity connected to depression may directly result from the mental illness itself and thus establish an animal model for additional exploration [20].

Epigenetic markers were previously used to determine various rating of depression in maltreated children. Weder et al performed a genome-wide methylation study in 94 maltreated and 96 healthy non-traumatized children with saliva-resultant DNA. Results showed that methylation in 3 genes were considered significant predictors of depression including Tubulin Polymerization Promoting Protein (*TPPP*), DNA-Binding Protein Inhibitor-3 (*ID3*), and Glutamate NMDA Receptor (*GRIN1*). These are biologically applicable with *TPPP* involved in neural circuitry growth, *ID3* involved in response to stress, and *GRIN1* involved in neural pliability suggesting epigenetic changes in these genes particularly with the combination of maltreatment may present risk for depression in children [21].

Furthermore, Motalvo-Ortiz et al validated the epigenetic changes of genes *GRIN1*, *ID3*, and *TPPP*. Secondary analysis was conducted using gene expression data obtained from medial prefrontal cortex (mPFC) tissue of mice that undergone a model of maternal neglect including early weaning (MSEW) and maternal separation. Depression-like phenotype data from using elevated plus maze (EPM), forced swimming tests (FST), and elevated plus maze (EPM) were also available. Results revealed gene expression of *ID3*, *TPPP*, and *GRIN1* in the mPFC to indicate behavioral alterations in the FST and EPM, thus further supporting the role of these genes in the depressive phenotypes following early life stress [22].

1.3 Inhibitor of DNA Binding/Differentiation and Environmental Pollutants

It was previously determined how ID3 may contribute to multifaceted ailments via metabolic distresses through environmental influence [18]. Additionally, ID3 also influences metabolic health & obesity in response to environmental stressors [44]. ID proteins have been seen linked to various types of EEDs such as PCBs, BPA, arsenic, and phthalates.

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Mechanisms reliable for initiating micro-vascular damage continue to be inadequately definite, while aspects such as oxidative stress induced by environmental toxicants have been suggested. Association in development of proliferative vascular lesions via increased neovascularization has been brought to attentiveness. Data has previously demonstrated how ROS via PCBs may contribute to neo-vascular phenotype progression with the objective of demonstrating the role of environmental toxicants in endothelial dysfunction with a focus on *ID3*. PCB-stimulated ROS intermediated neo-vascular phenotype furthermore depended on Pyk2 (Protein-tyrosine kinase 2) and *ID3*. Also, PCB153 treatment expanded endothelial spheroids' measurement with conditions that work on behalf of stem cell spheroid clonal selection. Higher ID3 protein expression matched with a greater quantity of oxidative DNA injury marker 8-OHdG in blood vessels. Overall, this shows the conceivable function of *ID3* in regulating micro-vascular lesion growth and vascular endothelial cell survival driven by environmental toxicants such as PCB153 [37-38]. Another study investigated how exposure to BPA stimulated reproductive anomalies in adult male testis. Adult C57/BI6 males were exposed to sesame oil, BPA, or diethylstilbestrol (DES) as a positive control from gestational days 10 to 16 and observed. Adult mRNA levels of genes associated with sexual maturation and differentiation, *ID2* and *GATA4*, were lower only in testes exposed to DES. At the molecular level, DES exposure via in utero, not BPA, leads to decreased mRNA gene expression connected with Sertoli cell differentiation [45].

Arsenic has also been seen to be involved with ID proteins. Arsenic exposure is known to be a risk factor for various cancers. Tsai et al aimed to investigate the contribution of *ID1* and connected signaling molecules in arsenic-mediated angiogenesis. The initial screening led to low arsenic contractions showing cellular responses including angiogenic activity and enhanced endothelial cell viability alongside increased *ID1* expression. Stimulated arsenic angiogenesis was suppressed in the ID1-knocked down cells compared to control cells. Additionally, angiogenic action and arsenic-stimulated expression of *ID1* showed mediated by PI3K/Akt, nitric oxide synthase (NOS), and NF-κB signaling. As a result, the data shows that *ID1* regulates angiogenesis supported by arsenic and *ID1* may be an anti-angiogenesis target for cancer associated with arsenic [46]. Furthermore, it was found that treatment with stress-stimulated metalloid arsenite, a chemical compound containing an arsenic oxoanion, led to accumulation of GFP-tagged *ID3* in the cytoplasm. Spaced N-terminal cysteine residues of *ID3* interacted with arsenic derivate phenylarsine oxide (PAO) and showed importance for arsenite-produced cytoplasmic accumulation, which suggests that arsenite induces CRM1-dependent nuclear export of *ID3* via binding to N-terminal cysteines. Overall, this indicates that *ID3* may be involved in the

biological activities of arsenite [47].

Arsenic trioxide (ATO), an important oxide of arsenic is a main precursor to other arsenic compounds. It has shown to strongly induce differentiation and apoptosis in acute promyleocytic leukemia, alongside cell cycle arrest in most solid tumors. Zhang et al screened signaling pathways that are involved in antitumor mechanisms and molecules that contribute in the antitumor effects of ATO. Results demonstrated that after verification at the transcriptional and translational levels in 4 various cancer cells, *ID2* was identified as an ATO anti-tumor-connected protein. Furthermore, silencing of *ID2* may enhance ATO-stimulated cell proliferation inhibition in cancer cells [48]. Phthalates, which are also considered EEDs, are widely used in the production of plastic products and other consumer goods. In a study done by Yao et al, mono-(2-ethylhexyl) phthalate (MEHP) stimulates matrix metalloproteinase 2 (MMP2) expression in testicular embryonal carcinoma NT2/D1 cells however, has no important result on MMP9 expression. Additionally, MEHP treatment caused certain genes including *GJA1* (Gap junction protein-alpha 1), *VCL* (vinculin), and *ID1* (inhibitor of DNA-binding protein-1) to down-regulate, while *CLDN6* (claudin-6) and *CTNNB1* (beta 1-catenin) were up-regulated. Results showed that Yao et al provide insights into mechanisms that may account for modulating progression of cancer following exposure to phthalates [49].

2. Relationship between Environmental Toxicants and Depressive Disorders

Estrogenic endocrine disruptor exposure has been previously demonstrated in various animal and population studies with a focus on depression. PCBs have been connected with depressive symptoms. Data was collected from 178 individuals on two measurement time points. PCBs were analyzed in plasma through human bio-monitoring and depressive symptoms were validated via questionnaire. Results demonstrated noteworthy mediation over time for dioxin-like, higher-chlorinated, and lower-chlorinated PCBs. Positive connections between PCB exposures with depressive symptom severity was facilitated by the main dopamine (DA) metabolite homovanillic acid (HVA). Higher exposure was also linked with PCBs with lower concentration in urinary HVA. Overall, this indicates links with PCB exposure and higher depressive symptoms after one year is mediated by the DA metabolite HVA as a substitute for DA, which can help elucidate principal neurochemical mechanisms of PCB-related depressive symptoms [50]. Additionally, studies suggest that exposure to BPA may contribute to neurobehavioral problems in childhood, resultant of symptoms of anxiety and depression. Perera et al investigated the association of prenatal BPA, observing sex-focused differences in both depressive and anxiety

indications in children aged 10-12 years old. Important positive connections between symptoms of depression and anxiety and prenatal BPA were observed among boys but not girls aged 10-12 years old [51]. Similarly, BPA has also been addressed in animal studies investigating whether paternal BPA can affect emotions of male rats and their respected offspring. Eighteen adult rats (F0) received a BPA diet for 21 weeks and then mated with non-exposed females to produce offspring (F1). Behaviors were evaluated in various tests including forced swimming test, elevated-plus maze, and open-field test. Furthermore, their serum corticosterone was observed. Exposure to BPA stimulated higher anxiety behaviors in F0 rats. Paternal exposure led to higher anxiety behaviors in F1 females and aggravated depression behaviors in both sexes of F1 rats. This data suggests preconception paternal exposure to low dose BPA may stimulate transgenerational sex-focused deficiencies in adult rats [51].

There also has been a relationship between arsenic and depression. A sample of 223 women was previously gathered from five public services in Chile. Data associated to arsenic exposure and urine samples for inorganic arsenic assessments were collected during women's second trimester pregnancy. Results revealed that the depression history, physical perception, number of children, age, and stressful maternity were associated with postpartum score. Furthermore the score was also associated with inorganic arsenic in women older than 25 years old [52]. Additionally, evidence indicates that subchronic exposure to arsenic causes cerebral neurodegeneration, which leads to disturbances associated to psychiatric disorders such as depression. Chang et al assessed the effects of subchronic arsenic exposure on the depression- and anxiety-like behaviors in both normal mice and chemically stimulated mouse model of depression via reserpine pretreatment. Results showed that arsenic exposure for 4 weeks increased anxiety-like behaviors on higher plus maze and open field test in normal mice and 8 weeks of exposure increased depression-like behaviors on forced swimming test and tail suspension test in reserpine pretreated mice. This reveals how subchronic exposure to arsenic induces anxiety-like behavior, while increasing depression-like behavior in the mouse model of depression [53].

3. Genomic Interactions between Inhibitor of DNA Binding/Differentiation, Environmental Toxicants, and Depression

To justify how the combination of ID proteins and environmental toxicants may contribute to depressive dysfunction at genomic levels, we integrated various publicly accessible tools in order to help enhance our general understanding. We first used Comparative Toxicogenomic Database

(CTD) [54] to support our understanding of gene interactions with ID proteins, various EEDs (including: PCBs, BPA, arsenic, and phthalates), and depressive disorders. Genes were curated for each of the categories resulting in a common gene list using a venn diagram [55]. Figures 1 & 2 reveal the interacting genes between ID proteins, EEDs, and depression disorders. Results displays the overlapping 437 interacting genes among EEDs and 14 interacting genes between ID proteins, EEDs, and depression. Overlapping gene results are furthermore shown via Table 1. To add how significant these genes are, we used Kyoto Encyclopedia of Genes and Genomes Pathway to represent their genomic relation. We established that these 14 genes are represented in 33 molecular pathways [56]. The top 3 pathways are represented in Table 2 and it is revealed that each of these pathways have a role in depression and related ailments [57-61]. To validate that these 14 genes do interact and create a network, STRING database was used to help provide protein-to-protein interaction [62-63]. As demonstrated in Figure 3, STRING delivers supplementary evidence that these genes create a genomic network, thus elucidating the role of ID proteins and EED exposure on depression via associated interacting-genes.

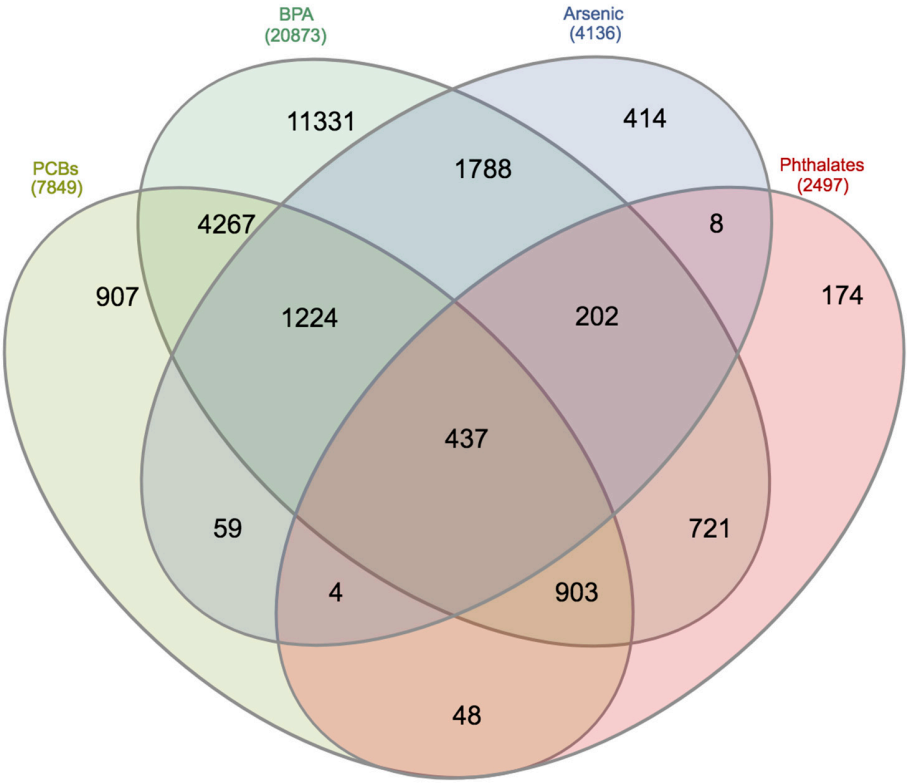

Figure 1. Venn diagram showing interacting genes between estrogenic endocrine disruptors (EEDs): Polychlorinated biphenyls (PCBs; 7,849 genes), Bisphenol A (BPA; 20,873 genes), Arsenic (4,136 genes), and Phthalates (2,497 genes). Results show 437 overlapping genes.

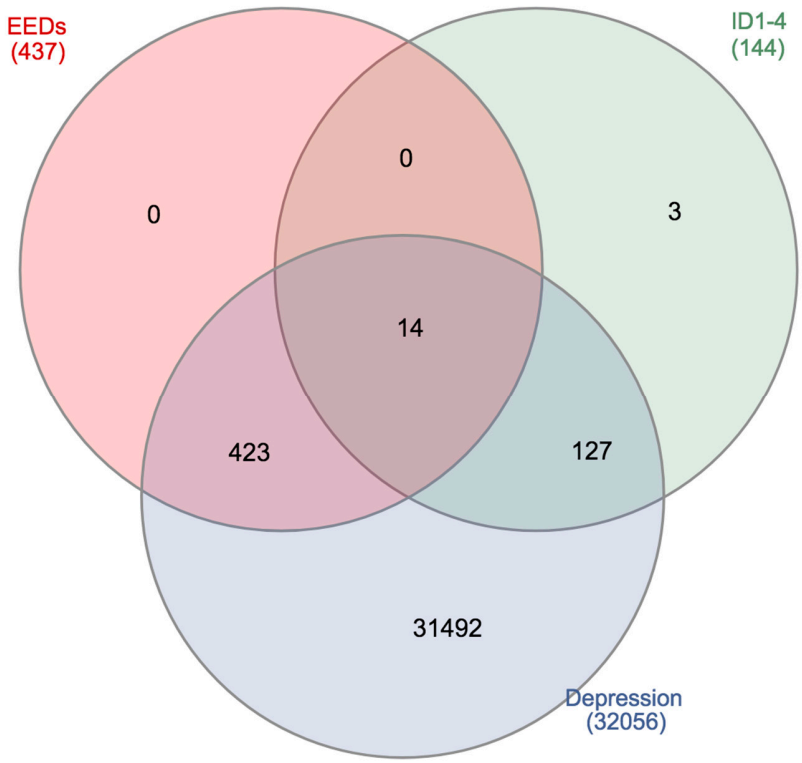

Figure 2. Venn diagram demonstrates interacting genets between overlapping estrogenic endocrine disruptors (EEDs; 437 genes), ID proteins (144 genes), and depression (32,056 genes). Results reveal 14 overlapping genes.

Table 1. Overlapping 14 interacting EED-ID protein-depression genes displayed below.

Gene Symbol	Gene Name
ATF3	Activating transcription factor 3
CDK2	Cyclin dependent kinase 2
ELOC	Elongin C
GATA4	GATA binding protein 4
HSPA1A	Heat shock protein family A (Hsp70) member 1A
HSPA5	Heat shock protein family A (Hsp70) member 5
HSPA8	Heat shock protein family A (Hsp70) member 8
HSPA9	Heat shock protein family A (Hsp70) member 9
ID1	Inhibitor of DNA binding 1, HLH protein
ID2	Inhibitor of DNA binding 2, HLH protein
ID3	Inhibitor of DNA binding 3, HLH protein
MAPK1	Mitogen-activated protein kinase 1

MAPK3	Mitogen-activated protein kinase 3
SREBF1	Sterol regulatory element binding transcription factor 1

Table 2. Top 3 pathways with 14 common overlapping genes with EEDs, ID proteins, and depression.

Pathway Name	Gene Count	P-Value	Genes
TGF-beta signaling pathway	5	9.34E-06	MAPK1, ID2, ID1, MAPK3, ID3
Signaling pathways regulating pluripotency of stem cells	5	7.04E-05	MAPK1, ID2, ID1, MAPK3, ID3
Estrogen signaling pathway	4	5.71E-04	MAPK1, MAPK3, HSPA1A, HSPA8

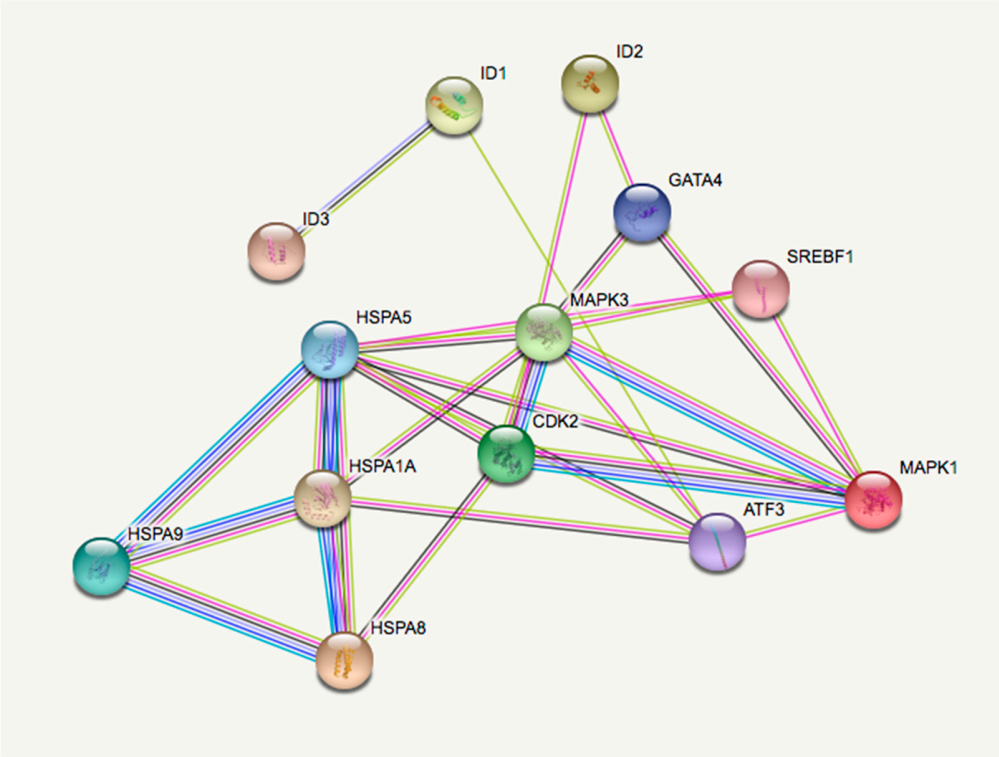

Figure 3. Gene network demonstrates fully connected structure between overlapping ID protein, EED, and depression genes.

4. Conclusion

Inhibitor of DNA-Binding/Differentiation proteins has presented to be connected with depression. Various studies have reported association between depression and EED exposure such as PCBs, BPA, arsenic, and phthalates. Based on evidence revealed in this review, we have shown that EED exposure may contribute to ID protein activation to modify molecular mechanisms, thus altering depressive dysfunction outcomes. Due to limited evidence caused by the novelty of this topic, it is essential to discuss limitation of this study by conducting further research to assess how exposure to EEDs and ID proteins play a function in depressive perturbations. Results from this will be beneficial in allowing

various public health & neurological professionals to uncover innovative opportunities that can be potentially used for prevention and treatment of these types of disorders and beyond.

Conflicts of Interest: The authors declare no conflict of interest

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