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Research Paper

Effects of Co-exposure to AhR Ligands and Lipopolysaccharides on RAW 264.7 Macrophage Polarization

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ABSTRACT

Background: Co-exposure to an aryl hydrocarbon receptor (AhR) agonist, such as benzo[a]pyrene (BaP) and lipopolysaccharides (LPS), commonly occurs through environmental pollution or smoking. The AhR plays a crucial role in macrophage polarization, influencing immune responses within the tumor microenvironment (TME). This study aimed to investigate how co-exposure to AhR ligands and LPS affects the balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophages.

Materials and Methods: RAW264.7 macrophages were treated with LPS (100 nM), BaP (2.5 µM), and CH-223191 (AhR antagonist, 1 µM), both individually and in combination. The polarization of RAW264.7 macrophages was assessed using flow cytometry and real-time polymerase chain reaction (PCR), focusing on the analysis of surface markers CD80 and CD206, as well as the gene expression levels of *iNOS*, *Arg1*, and *CD206*. Enzyme-linked immunosorbent assay (ELISA) was utilized to measure IL-10 and TNF-α secretion.

Results: Combining LPS with BaP or CH-223191 altered macrophage surface marker expression, increasing a population positive for both M1 and M2 markers. LPS significantly upregulated *iNOS* expression, whereas co-treatment with BaP or CH-223191 attenuated this effect. Co-exposure to BaP and LPS reduced *Arg1* expression relative to LPS alone, while co-treatment with CH-223191 and LPS increased *CD206* expression. LPS treatment alone, or in combination with BaP or CH-223191, increased TNF-α levels. IL-10 secretion increased only in the CH-223191+LPS group.

Conclusion: These findings suggest that co-exposure to BaP and LPS promotes a complex macrophage activation state characterized by strong pro-inflammatory cytokine secretion but altered marker expression, whereas CH-223191 modulates this response differently.

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Introduction

Environmental exposure to toxicants, particularly polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene (BaP), has been implicated in the development of various cancers, including breast cancer [1]. BaP, a group 1 carcinogen [2], is commonly found in cigarette smoke, vehicle exhaust, deep-fried foods, and industrial emissions [3]. Notably, BaP concentrations in the sidestream smoke of cigarettes range from 52 to 95 ng per cigarette, which is more than three times higher than in mainstream smoke [4]. Epidemiological studies, including findings from the French E3N cohort, have identified a correlation between airborne BaP exposure and increased breast cancer incidence [5], emphasizing the need for further investigation into its biological effects.

The outer membrane of most gram-negative bacteria contains lipopolysaccharide (LPS), also known as endotoxin. LPS is commonly present in agricultural environments and in particulate matter (PM 2.5) [6]. It is recognized for its ability to activate toll-like receptors (TLRs) on innate immune cells, particularly macrophages. This activation triggers inflammatory responses that can influence tumor progression [7]. Smoking one pack of cigarettes per day results in exposure to approximately 2.5 µg of respirable LPS- a dosage comparable to the levels associated with adverse health effects in cotton textile workers [8]. Although no universally accepted exposure threshold for endotoxins currently exists, the Netherlands' National Health Council has proposed a limit of 90 EU m^{-3} [9]. Importantly, the aryl hydrocarbon receptor (AhR) has been shown to regulate inflammatory gene expression triggered by LPS [10].

The AhR plays a key role in regulating responses to both BaP and LPS. CH-223191 is a synthetic and selective antagonist of AhR. Unlike some earlier AhR antagonists, CH-223191 lacks agonistic properties, making it a reliable compound for selectively blocking AhR-dependent signaling pathways. Activation of AhR by BaP modulates inflammatory signaling and influences macrophage polarization, thereby impacting the tumor microenvironment (TME) [2, 11]. Tumor-associated macrophages (TAMs) exhibit considerable plasticity, differentiating into either M1 or M2 phenotypes. M1 macrophages enhance anti-tumor immunity by producing cytokines, such as interleukin (IL)-6, IL-12, IL-23, and tumor necrosis factor alpha (TNF-α) in response to Th1 stimuli, like IFN-γ or LPS. In contrast, M2 macrophages promote tumor progression, invasion, and immune evasion, with activation driven by Th2 cytokines [IL-4, IL-13], glucocorticoids, and immune complexes. M2 macrophages are typically identified by the markers CD206 and CD163 [12]. Understanding the interaction between macrophage polarization and environmental pollutants, like BaP and LPS is crucial for elucidating their combined impact on cancer progression [13].

Despite comprehensive studies on macrophage polarization and the impact of environmental pollutants on cancer, the interplay between BaP and LPS in shaping macrophage behavior remains poorly understood. Most research has focused either on the inflammatory effects of LPS or the carcinogenic properties of BaP independently. However, their combined influence on macrophage polarization has not been adequately explored.

This study aimed to investigate the co-exposure effects of AhR ligands and LPS on RAW264.7 macrophage polarization. Given that BaP activates AhR, which in turn regulates macrophage polarization and inflammatory responses, understanding this interaction is essential for elucidating how environmental pollutants alter immune dynamics and contribute to cancer progression.

Materials and Methods

Cell culture

The RAW264.7 cell line (a murine macrophage cell line derived from BALB/c mice) was obtained from the Iranian Biological Resource Center (Tehran, Iran). Cells were cultured in high glucose Dulbecco's modified eagle medium (DMEM) (4.5 g/L) supplemented with 10% fetal bovine serum (FBS) (Biowest, France) and 1% antibiotic (penicillin/streptomycin, Biowest, France). Cultures were maintained at 37 ˚C in a humidified atmosphere containing 5% CO_2.

Measurement of BaP cytotoxicity

BaP (Alfa Aesar, Karlsruhe, Germany) was dissolved in dimethyl sulfoxide (DMSO) to prepare a stock solution and stored at –20 ˚C. Prior to use, the stock was thawed and diluted with culture medium, ensuring that the final DMSO concentration remained below 0.1%. RAW264.7 cells were seeded in 96-well plates (1×10^4 cells/well). After 24 hours, the medium was replaced with fresh medium containing varying concentrations of BaP (0.5, 1, 2.5, 5, 10, and 50 µm). Following 48 hours of incubation, MTT solution (5 mg/mL, Sigma-Aldrich) was added to each well, and cells were incubated for an additional 4

hours. The optical density (OD) was measured at 570 nm using a microplate reader (BioTek, ELx808).

Flow cytometry

Flow cytometry was employed to analyze surface marker expression and assess macrophage polarization. Cells were seeded in a 6-well plate (3×10^5 cells/well) and incubated for 24 hours. The cells were then exposed to LPS (100 nM), BaP (2.5 µM), and CH-223191 (1 µM), or their combination for 24 hours. After treatment, the supernatant was discarded, and the cells were collected and centrifuged. They were then incubated for 30 minutes with fluorescently labeled antibodies: PE anti-mouse CD80 (Clone 16-10A1; 1:200) and PE/Cyanine7 anti-mouse CD206 (Clone C068C2; 1:200). Flow cytometric analysis was performed using a BD FACSCalibur, and data were analyzed with FlowJo software.

Quantitative polymerase chain reaction (qPCR)

qPCR was used to assess the expression of macrophage-related genes. *iNOS* was analyzed as an M1 marker, while *Arg1* and *CD206* were analyzed as M2 markers. RAW264.7 cells were seeded and exposed to LPS, BaP, and CH-223191, or their combination, as described previously in the flow cytometry experiments. Total RNA was extracted using Trizol (Biobasic, Canada) according to the manufacturer's instructions. The quality and concentration of the extracted RNA were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific), after which cDNA was synthesized using a cDNA synthesis kit (Bio Basic, Canada). qPCR was performed on a StepOnePlus instrument (Applied Biosystems). The ΔΔCt method was used to calculate the relative mRNA expression of target genes, with *GAPDH* serving as the internal control. The primers (Pishgam Bitotech, Iran) used in the study are listed in Table 1.

Cytokine quantification

RAW264.7 cells were seeded in a 6-well plate (3×10^5/well). After 24 hours, the cells were treated as described previously. Supernatants were collected after 48 hours and stored at −20 ˚C. TNF-α and IL-10 levels were measured using Enzyme-linked immunosorbent assay (ELISA) kits (eBioscience). Results are presented as Mean±SD (n=3).

Statistical analysis

Data were analyzed using GraphPad Prism software, version 8 and expressed as Mean±SD. A one-way ANOVA followed by Tukey's post hoc test was used for multiple comparisons. A $P<0.05$ was considered statistically significant.

Results

BaP decreased cell viability in Raw264.7 cells

Exposure to BaP for 48 hours induced cytotoxic effects, reducing the survival of RAW264.7 cells. BaP exhibited toxicity at concentrations as high as 10 µM ($P<0.01$), with a more pronounced effect at higher doses ($P<0.001$, Figure 1). Based on these results and our previous studies, a concentration of 2.5 µM was selected for all subsequent experiments [14].

Expression of M1/M2 macrophage markers after treatment with LPS, AhR ligands, and their combination in RAW 264.7 macrophages

As shown in Figure 2, LPS treatment significantly increased the population of macrophages expressing both M1 and M2 surface markers compared to the control group (Figures 2A and 2B). Treatment with BaP or CH-223191 alone reduced the proportion of these double-positive macrophages relative to LPS treatment. Moreover, co-treatment of LPS with AhR ligands decreased the population of unpolarized (M0) macrophages while increasing the population of macrophages expressing

Table 1. The primers used in the study

Gene	Forward (5´→3´)	Reverse (5´→3´)
iNOS	TCACCTTCGAGGGCAGCCGA	TCCGTGGCAAAGCGAGCCAG
Arg1	CCACAGTCTGGCAGTTGGAAG	GGTTGTCAGGGGAGTGTTGATG
CD206	CTCTGTTCAGCTATTGGACGC	CGGAATTTCTGGGATTCAGCTTC
GAPDH	TGTGATGGGTGTGAACCACG	CAGTGAGCTTCCCGTTCAGC

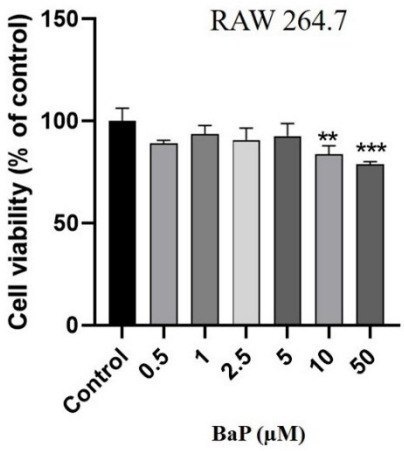

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Figure 1. Effects of BaP on the viability of RAW264.7 cell lines

**P<0.01 and ***P<0.001 compared to the control group.

Note: Cells were seeded and treated as described in the methods section.

both M1 and M2 markers compared to LPS treatment alone.

M1/M2 macrophage marker gene expression in RAW264.7 cells after treatment with LPS, AhR ligands, and their combination

As shown in Figure 3A, treatment with BaP or CH-223191, acting as an AhR agonist and antagonist, respectively, did not significantly alter *iNOS* gene expression. However, LPS treatment markedly upregulated *iNOS* expression relative to the control group (P<0.001). Co-exposure to LPS with BaP or CH-223191 significantly reduced *iNOS* expression compared to LPS alone. Regarding *Arg1* expression (Figure 3B), BaP treatment led to a significant decrease (P<0.05), while LPS exposure increased *Arg1* expression (P<0.001). Notably, co-exposure to LPS and BaP further suppressed *Arg1* expression compared to LPS alone (P<0.001). For *CD206* expression (Figure 3C), BaP alone had no significant effect. However, treatment with CH-223191, LPS, and their combination significantly downregulated *CD206* expression relative to the control group (P<0.001).

TNF-α and IL-10 levels

As shown in Figure 4A, TNF-α levels were significantly elevated in the LPS, LPS+BaP, and LPS+CH-223191 groups compared to the control (P<0.001). However, IL-10 levels remained unchanged following individual treatments compared to the control. Interestingly, co-exposure to LPS and CH-223191 increased IL-10 levels (P<0.05), whereas co-exposure to LPS and BaP decreased IL-10 levels compared to LPS alone (Figure 4B, P<0.05).

Discussion

While research on macrophage polarization has advanced, several aspects remain incomplete or contentious. The dual role of TAMs as both pro-tumor and anti-tumor agents highlights the significant influences of macrophage polarization on their functional characteristics [15]. Our results showed that LPS treatment significantly upregulated *iNOS* expression; however, this effect was attenuated when cells were co-treated with either BaP or CH-223191. Co-exposure to BaP and LPS reduced *Arg1* expression compared to LPS treatment alone, whereas co-treatment with CH-223191 increased *CD206* expression. TNF-α levels were elevated following LPS treatment. IL-10 secretion increased only in the CH-223191+LPS treatment group.

Although low doses of BaP did not affect RAW264.7 cell viability, van Grevenynghe et al. demonstrated that BaP can disrupt the differentiation of monocytes to macrophages [16]. Sada-Ovalle et al. reported that BaP, at 1 and 5 μg/mL, decreased CD80 expression in THP-1 cells, while 20 μg/mL increased it [17]. Additionally, RAW264.7 cells treated with LPS at various concentrations and time points showed significantly elevated CD80 expression [18, 19]. Fueldner et al. found that a low dose of BaP (800 nM) did not affect the expression of CD86 in murine bone marrow-derived macrophages, but stimulation with killed *Salmonella* bacteria (hk.S.E) increased CD86 expression in an AhR-dependent manner, as AhR-deficient cells lacked this response [20]. BaP at 800 nM enhanced *iNOS* expression in stimulated cells but not in AhR-/-macrophages. In our study, BaP

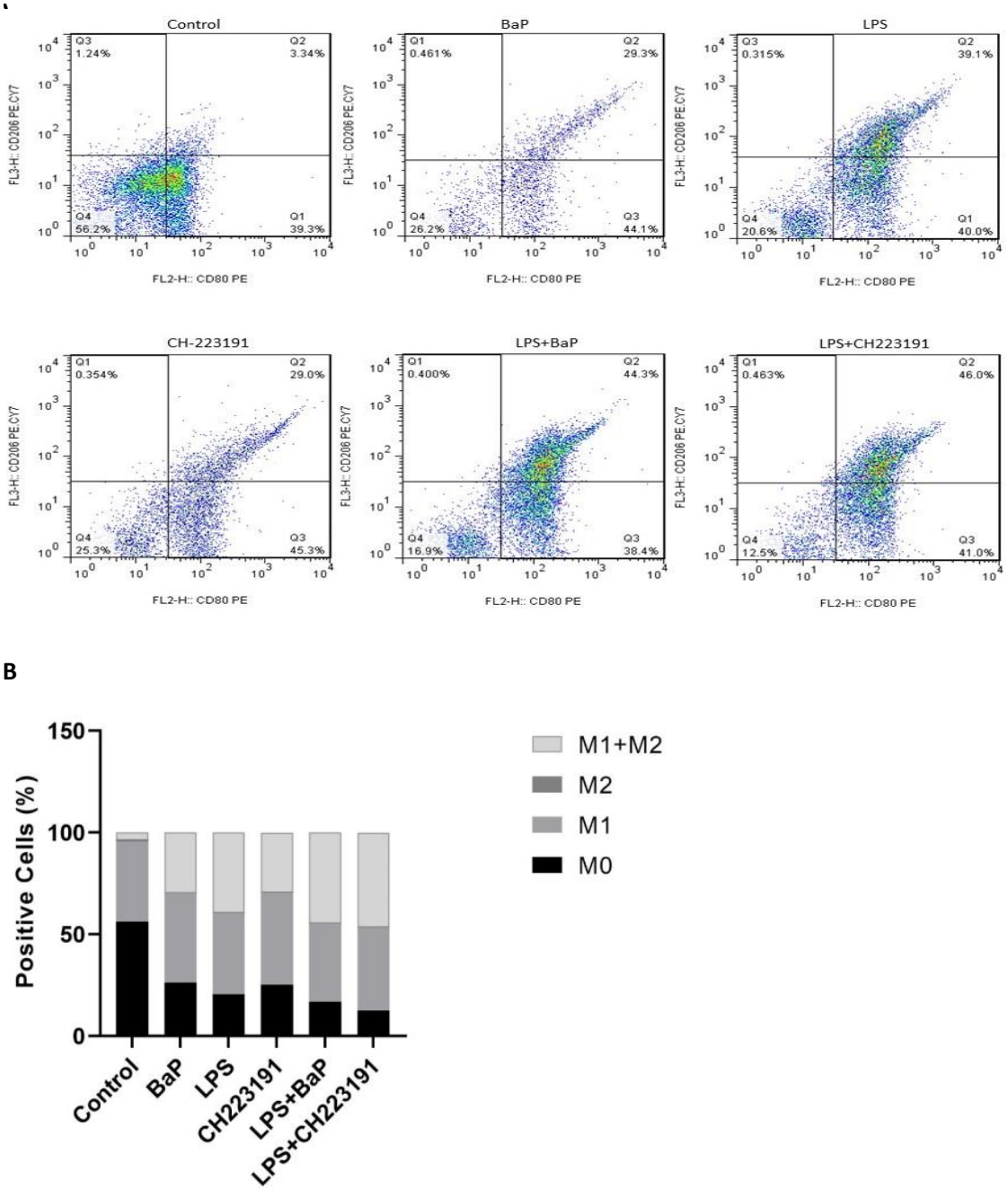

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Figure 2. Flow cytometric analysis of macrophage surface markers in RAW264.7 cells **(**A), the cells were exposed to LPS (100 nM), BaP (2.5 µM), and CH-223191 (1 µM), individually and in combination (LPS+BaP, LPS+CH-223191), and then the expression of CD80 (M1) and CD206 (M2) markers was analyzed by flow cytometry (B). (M0, Q4; M1, Q3; M2, Q1 and M1 and M2, Q2).

at 2.5 µM did not increase *iNOS* gene expression when administered alone.

Furthermore, spleen macrophages exposed to BaP at 15 µM showed no changes in iNOS and Arg1 proteins levels; however, co-treatment with dibutyl phthalate (30 µM) upregulated iNOS and downregulated Arg1 expression [21].

Several studies suggest that PAHs can bias macrophages toward the M1 phenotype [22]. Consistent with this, AhR inhibition in the presence of LPS (CH-223191+LPS) enhances the expression of M2 associated-genes, such as *Arg1* and *CD206*, compared to BaP+LPS treatment. LPS at 100 nM significantly increased *iNOS* expression, while BaP and CH-223191 co-treatment reduced it. In microglia activated by LPS, Lee et al. demonstrated that, without

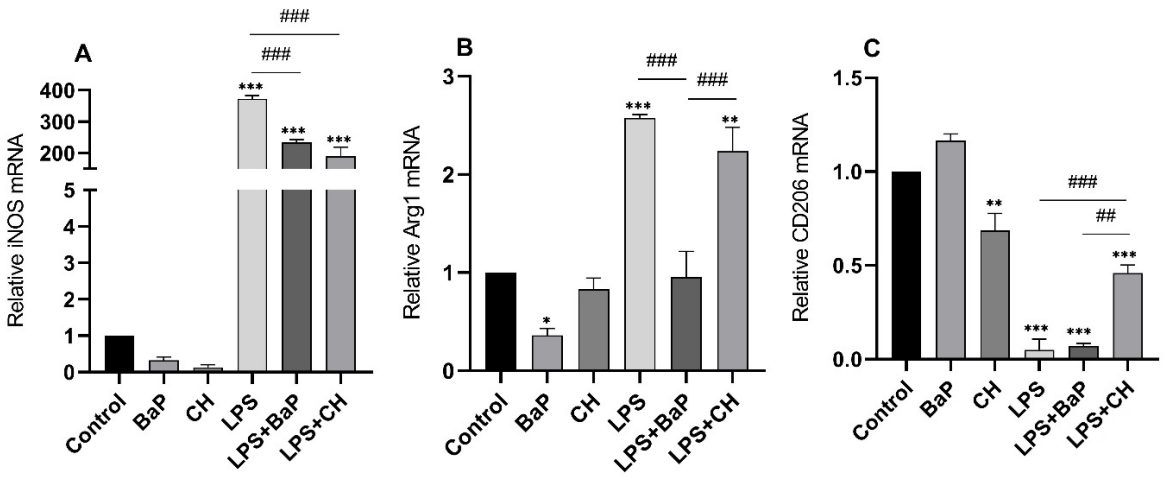

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Figure 3. Effects of LPS and AhR ligands BaP and CH-223191 on the expression of *iNOS* (A), *Arg1* (B), and *CD206* (C) in RAW264.7 cells

*P<0.05, **P<0.01, and ***P<0.001 compared to the control group, ##P<0.01 and ###P<0.001 compared to the LPS group.

Note: Cells were treated with LPS (100 nM), BaP (2.5 μM), and CH-223191 (1 μM), individually or in combination, for 24 hours and mRNA expression levels of *iNOS*, *Arg1*, and *CD206* were analyzed by quantitative PCR.

external AhR ligands, AhR promotes pro-inflammatory effects by targeting DRE-containing genes, like *iNOS*, rather than NF-κB binding sites. However, exposure to AhR ligands, such as FICZ and 3-Methylcholanthrene, enhances AhR activity but attenuates immune responses via co-recruitment of AhR and NF-κB to the NFα-κB site, reducing AhR binding to DRE-containing genes [23]. AhR also modulates cytokine production, reducing pro-inflammatory cytokines while enhancing anti-inflammatory cytokines, such as IL-10 [23]. Consequently, AhR-deficient mice exhibit increased susceptibility to LPS-induced septic shock [24].

Since M1 macrophages are the primary producers of TNF-α, an increase in TNF-α levels was expected following LPS exposure. However, BaP and CH-223191

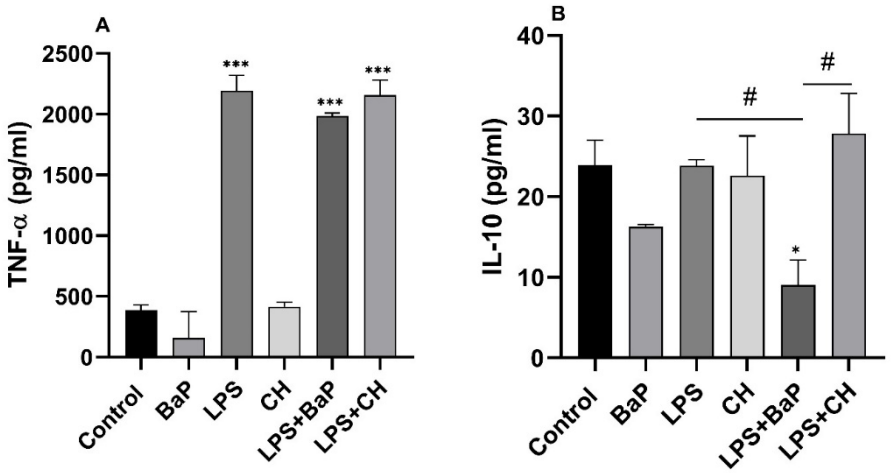

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Figure 4. Effects of LPS and AhR ligands on TNF-α (A) and IL-10 (B) levels in RAW264.7 cells

*P<0.05 and ***P<0.001 compared to the control group, #P<0.05 compared to the LPS group.

Note: Cells were treated with LPS (100 nM), BaP (2.5 μM), and CH-223191 (1 μM), individually or in combination, for 48 hours. TNF-α and IL-10 levels were measured using ELISA.

treatment alone did not significantly alter TNF-α levels compared to control. Previous studies reported that BaP at 15 μM in spleen macrophages or 2 μM in human macrophages did not increase TNF-α secretion [21, 24]. Additionally, BaP activated by hk.S.E reduced TNF-α production in an AhR-dependent manner [20]. Experimental evidence also indicates that the combination of BaP and LPS decreases TNF-α while increasing IL-10 [20]. Kimura et al. showed that AhR regulates the production of pro-inflammatory cytokines after LPS stimulation independently of IL-10 [25]. Therefore, the observed downregulation of IL-10 after BaP+LPS treatment, relative to LPS alone, likely involves an alternative signaling pathway. The increased IL-10 secretion in the LPS+CH-223191 group may result from AhR pathway suppression. Tong et al. demonstrated that resveratrol, a natural AhR inhibitor, reduces IL-8, IL-6, and TNF-α by inhibiting the NF-κB/MAPK signaling, while simultaneously increasing IL-10 levels [26]. Rojas et al. evaluated the effects of PAHs on immune cytokines, finding that 10, 30, and 50 μg/mL of PAHs significantly elevated TNF-α at all concentrations, while IL-10 increased only at 30 μg/mL [27]. Another study with RAW264.7 cells exposed to LPS (1 μg/mL) and pyrene (1-20 μg/mL) showed a significant increase in TNF-α in both the LPS group and the 10 μg/mL pyrene group [17].

Conclusion

Our results suggest that co-exposure to environmental pollutants, such as BaP and inflammatory stimuli, like LPS significantly modulates macrophage behavior, promoting a complex activation state characterized by elevated pro-inflammatory cytokine secretion and altered marker expression. In contrast, AhR antagonism via CH-223191 modulates this response differently, notably by increasing IL-10 secretion and M2 marker expression. These results highlight the intricate interplay between environmental factors and immune regulation, underscoring the need for further investigation into macrophage polarization mechanisms and their implication for chronic inflammation and cancer progression.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

The present study was extracted from the master's thesis of Parsa Abbaszadeh, approved by the Department of Toxicology, Faculty of Medial Sciences, Tarbiat Modares University, Tehran, Iran.

Authors' contributions

Conceptualization: Amir Shadboorestan and Sara Soudi; Methodology, Writing and final approval: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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