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Scientific paper

Immunomodulatory Role of Palladium(II) Complex with Ethyl Derivative of Thiosalicylic Acid Ligand

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Abstract

Many complexes have shown antitumor potential, including the bis(*S*-ethyl-2-thiosalicylate)palladium(II) complex. The aim of this study was to investigate potential immunomodulatory effects of this complex on acquired and innate immunity, *in vitro*. The effect was assessed based on the levels of cytokines tumor necrosis factor alpha (TNF-α), interleukin (IL) 1β, interferon gamma (IFN-γ), IL-17 and IL-10. Cytokine concentrations were measured by ELISA assay. Pd(II) complex led to a reduced secretion of most pro-inflammatory cytokines. The effects of the complex were more intense in non-activated cells. The same effect was shown in cells of acquired and innate immunity. These effects make the Pd(II) complex not only a potential antitumor agent, but also an anti-inflammatory agent.

Keywords: immunomodulation; acquired and innate immune cells

1. Introduction

Carcinomas represent abnormal and uncontrolled growth of cells, and in addition to cardiovascular diseases, they are the leading cause of death in 127 countries.[1,2] Since the discovery of cisplatin, as the first complex compound used in the treatment of cancer, complex compounds have become the subject of the research. Cisplatin leads to numerous side effects such as: immunosuppression, allergic reactions, kidney damage, gastrointestinal symptoms, bleeding and hearing loss. Another side effect that mostly led to the research of complexes based on other metals is the non-selectivity of cisplatin, the manifestation of a cytotoxic effect on both healthy and cancer cells.[3,4] Non-platinum complexes showed excellent antitumor potential, as well as reduction of side effects. In addition, certain complexes have shown prevention of tumor cell migration and metastasis. One of the tested metals in this group is palladium. Palladium shows a significantly lower level of toxicity and fewer side effects.[3] Also, palladium(II) has similar structural and thermodynamic characteristics as platinum(II).[5,6] The complexes of palladium with sulfur, nitrogen and numerous other ligands tested so far have shown antibacterial, antiviral and antifungal effects. One of the ligands that can be combined with the palladium(II) ion is thiosalicylic acid. This ligand has beneficial effects on inflammation, allergic processes and respiratory symptoms. It also shows beneficial effects in the treatment of cancer, such as melanoma.[7–9] Complexes based on palladium with S-donor chelating ligands have been studied and have shown numerous biologically relevant activities. Many palladium complexes possess promising cytotoxic effects on A549, HepG2, MDA-MB231, HCT-116, Ca-Co-2, HeLa, and numerous other cell lines, suggesting their potential as candidates for further studies in cancer treatment.[10–15] In addition, these complexes have shown significant antimicrobial effects on several pathogens, including *E. faecalis*, *S. aureus*, *E. coli*, *K. pneumoniae*, *P.*

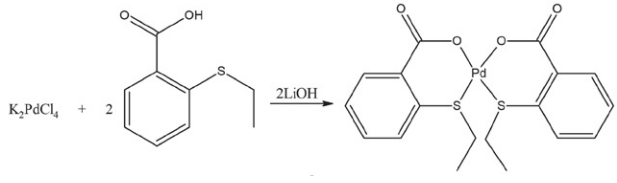
aeruginosa, and *Aspergillus* species.[7,10] Antiamoebic activity on *E. histolytica* was also observed.[16] Previous studies of palladium complexes have shown a proapoptotic effect, but also DNA molecule damage as well as mitochondrial depolarization, which represents their potential role in cellular damage.[17] Research on palladium complexes has led to the application of a palladium complex, known as padeliporfin (TOOKAD®), in clinical practice.[18]

One of the previously conducted studies investigated the biological activity of palladium complexes with thiosalicylic acid derivatives, of which the *bis*(*S*-ethyl-2-thiosalicylate)palladium(II) complex was singled out as the complex with the highest cytotoxic potential. Its effect was demonstrated by *in vitro* testing on the following cell lines: CaCo-2 (human colorectal adenocarcinoma cells), HCT-116 (human colon cancer cells), A549 (adenocarcinomic human alveolar basal epithelial cells).[12] Based on the reported cytotoxic effect on tumor cells, *bis*(*S*-ethyl-2-thiosalicylate)palladium(II) complex could represent a potential cancer therapy. Our goal was to determine the immunomodulatory effect of this compound.

2. Experimental

2. 1. Synthesis of the *bis*(S-ethyl-2-thiosalicylate)palladium(II)-complex, [Pd(S-et-thiosal)$_2$]

The production process of complexes based on thiosalicylic acid derivatives has already been described in previously published articles, so the same process was used for this research.[7,12] The first step in the synthesis of the [Pd(*S*-et-thiosal)$_2$] complex involves the preparation of a solution of $K_2[PdCl_4]$, by dissolving 0.100 g (0.3065 mmol) of the mentioned compound in 10 mL of water on a steam bath. To the previously prepared solution, 0.1117 g (0.613 mmol) of S-ethyl-2-thiosalicylic acid is added. The resulting mixture is stirred for a period of 2 h. During this period, a solution of LiOH, obtained by dissolving 0.0256 g (0.613 mmol) of the hydroxide in 10 mL of water, is gradually added to the stirred solution (Scheme 1). The result of the whole process is the complex, obtained as a precipitate, which is filtered, washed first with water to remove water-soluble impurities, such as excess metal ions (e.g., Pd^{2+}), anions from the metal salts, as well as small amounts of unreacted polar reagents, and then rinsed with ether to eliminate residual organic impurities, such as unreacted ligands, organic by-products, and traces of organic solvents such as ethanol and then dried in air. The content of the obtained product was determined by elemental microanalysis, IR as well as NMR (^{1}H and ^{13}C).



Scheme 1: Synthesis of the [Pd(S-et-thiosal)$_2$]

2. 2. Isolation and ConA/LPS Priming of Splenocytes

The isolation of splenocytes was conducted as previously described.[19] Briefly, the spleens extracted from BALB/c were minced in RPMI 1640 (Sigma-Aldrich, St. Louis, MO, USA) and forced gently through a 40 μm cell strainer nylon mesh using a sterile syringe plunger and centrifuged at 400 g for 5 min. Pelleted spleen cells were incubated in 2 mL of lysis buffer, followed by incubation for five minutes on ice. Cells were further centrifuged at 400 g for 5 min and resuspended in RPMI 1640 with 10% FBS, penicillin-streptomycin (1 mmol/L), mixed nonessential amino acids (1 mmol/L) and L-glutamine (2 mmol/L). Total number of cells was determined using trypan blue exclusion on a hemocytometer and cells were used for further analysis. Isolated splenocytes were placed in a microtiter plate and divided into six groups: cells treated with medium only (control group), cells treated with Concanavalin A – ConA (0.5 μg/mL), cells treated with LPS from E. coli 055:B5 (0.5 μg/mL), cells treated with the Pd(II) complex, cells treated simultaneously with ConA and the Pd(II)-complex and cells treated simultaneously with LPS and the Pd(II) complex. The dose of the Pd(II) complex used in all *in vitro* experiments was established on a previously determined IC_{50} value.[12] Cells with viability higher than 95% were used in all experiments. The isolated cells were plated in 96-well microtiter plates followed by incubation for 24h ($2{\cdot}10^5$ cells per well). Cells were incubated at 37 °C in a humidified atmosphere of 5% CO_2 and 95% air. The trypan blue assay confirmed cell viability of over 90% after incubation. There was no difference in viability between groups.

2. 3. Assessment of Cytokine Concentration

After incubation, the cells were centrifuged, and the supernatant was used for further testing. To assess cytokine concentration, ELISA assay kits from R&D Systems (Minneapolis, MN, USA) were used as specified by the manufacturer. During this study, the concentration of TNF-α, IL-1β, IFN-γ, IL-17, and IL-10 was measured.

2. 4. Statistical Data Processing

SPSS program (version 22.0) was used for statistical data processing. The obtained data were analyzed by Student's t-test, Mann-Whitney U test, or Kruskal-Wallis test. Data are expressed as Mean ± standard error of the mean for each group. The difference was considered significant when $p < 0.05$.

3. Results and discussion

3. 1. Palladium(II) Complex Managed to Decreased Concentration of Pro-inflammatory Mediators Potentially by Affecting Acquired Immune Response

Our first goal was to evaluate cytokine production in splenocytes after ConA, Pd(II) complex and cotreatment. ConA, was used as an activator of acquired immunity cells in order to reveal the effect of Pd(II) complex on activated and non-activated cells. Con A, a lectin, is one of the activators of T cells that are an integral part of acquired immunity, and it achieves its effect by binding to glycoproteins and carbohydrates.[20,21] As expected, ConA led to a significant increase in TNF-α, IL-1β, IL-17, IFN-γ and IL-10 compared to untreated cells ($p < 0.05$) (Figure 1A). Pd(II) complex, also induced the production of pro-inflammatory cytokines TNF-α ($p < 0.05$) and IL-1β ($p < 0.05$), as well as the pro-Th1 cytokine IFN-γ ($p < 0.05$), the pro-Th17 cytokine IL-17 ($p < 0.05$) and anti-inflammatory cytokine IL-10 ($p < 0.05$) in splenocytes compared to untreated cells (Figure 1A). Application of ConA and Pd(II) complex led to a decrement in concentration of IL-1β ($p < 0.05$), IL-17 ($p < 0.05$), IFN-γ and IL-10 (did not reach statistical significance) compared to ConA treatment only (Figure 1A). In continuation of this study, we analyzed the ratio of counter-regulatory cytokine concentrations in order to confirm the predominance of pro- or anti-inflammatory cytokines. ConA treatment led to decrement in the ratio of TNF-α/IL-10, IL-1β/IL-10, IL-17/IL-10 and IFN-γ/IL-10 compared to untreated cells ($p < 0.05$) (Figure 1B). Pd(II) complex also leads to a significant reduction in all observed ratios of pro-inflammatory (TNF-α, IL-1β, IFN-γ, IL-17) and anti-inflammatory cytokines (IL-10) compared to non-activated cells ($p < 0.05$) (Figure 1B). Cotreatment with ConA and Pd(II) complex led to a decrement in ratio of IL-1β/IL-10 ($p < 0.05$), IL-17/IL-10 ($p < 0.05$), and IFN-γ/IL-10 (did not reach statistical significance) compared to ConA treated cells (Figure 1B). Cotreatment, also led to a significant increase in the ratio of TNF-α/IL-10 ($p < 0.05$) (Figure 1B). When analyzing the effect of the complex in relation to the activation status of target cells, increased ratio of TNF-α, IL-1β, IL-17, IFN-γ and IL-10 con-

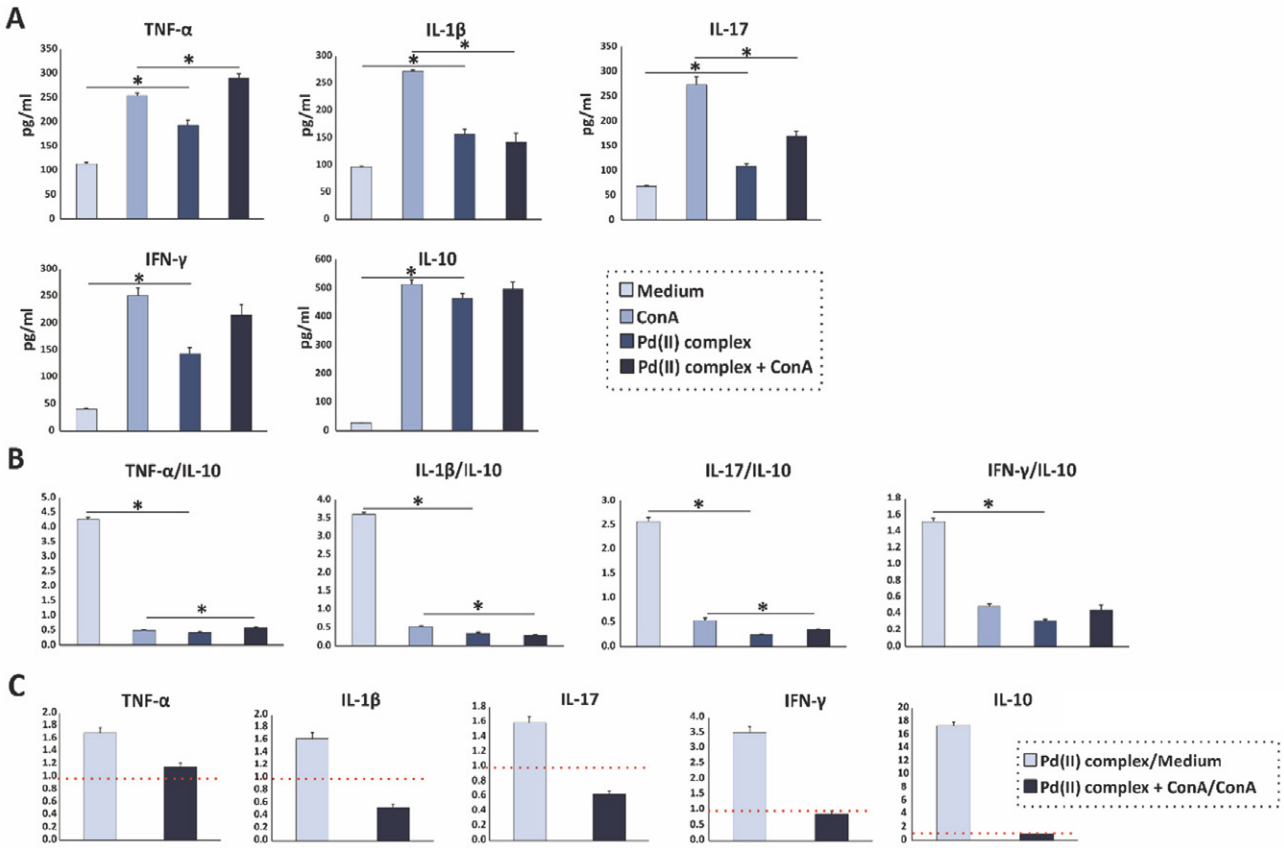


Figure 1: Cytokine production due to Pd(II)-complex treatment in Con-a primed splenocytes (A) The concentration of cytokines produced by splenocytes incubated with medium only, ConA, Pd(II) complex or a combination of Pd(II) complex and ConA. The concentration of TNF-α, IL-1β, IL-17, IL-10 and IFN-γ were determined by ELISA. **(B)** Ratio of pro- and anti-inflammatory cytokine concentrations produced by splenocytes incubated with medium only, ConA, Pd(II) complex or a combination of Pd(II) complex and ConA. **(C)** Ratio of cytokine production- unstimulated (Pd(II)-complex/medium) and stimulated cells (Pd(II)-complex + ConA/ConA). The data are shown as mean ± SEM. Statistical significance was tested by the Mann-Whitney U test and Student's t-test, where appropriate. (*$p < 0.05$).

centration in Pd(II)-complex treated against medium only was detected. The ratio of same cytokines concentrations in Pd(II)-complex+ConA treated against ConA only was significantly lower (Figure 1C).

Presented data revealed immunomodulatory role of Pd(II) complex on freshly isolated splenocytes. Although Pd(II) complex itself exhibits activating properties on non-primed cells, by enhancing the production of all cytokines of interest, its effect on activated (ConA primed) cells is quite the opposite, resulting in reduced cytokine production. As ConA is a pan-activator of T lymphocytes, we assume that the effect of the Pd(II) complex on ConA-primed cells is primarily an effect on activated T lymphocytes. Given that activated T lymphocytes are producers of pro-inflammatory cytokines in many acute and chronic pathological conditions,[22,23] we believe that usage of Pd(II) complex would have a beneficial effect on inflammatory conditions as well as on autoimmune diseases. And yet our results clearly show that the complex exhibits a more significant effect on non-primed cells, which may be innate immune cells in the spleen.

3. 2. Palladium(II) Complex Acts as a Potent Activator of Myeloid Cells

We further used lipopolysaccharide (LPS) as a cell activator in experiments examining immunomodulatory capacity of Pd(II) complex. LPS is an integral part of the outer membrane of gram-negative bacteria, which leads to increased secretion of numerous cytokines by monocytes, both in humans and mice.[24] It is a molecule that can trigger a strong inflammatory response when detected by the innate immune cell receptors, specifically CD14 and Toll-like receptors type 4 (TLR4).[25,26] In order to determine whether Pd(II) complex affected capacity and immunomodulatory properties of LPS primed and non-primed splenocytes, production of various cytokines (IL-1β, TNF-α, IFN-γ, IL-17 and IL-10) was evaluated. Consistent with expectations LPS stimulation elicited a significant up-regulation in the secretion of TNF-α, IL-1β, IFN-γ, IL-17 and IL-10 compared with non-activated cells ($p < 0.05$) (Figure 2A). The combination of Pd(II) complex and LPS led to decrease in value of IL-1β ($p < 0.05$), IFN-γ ($p <$

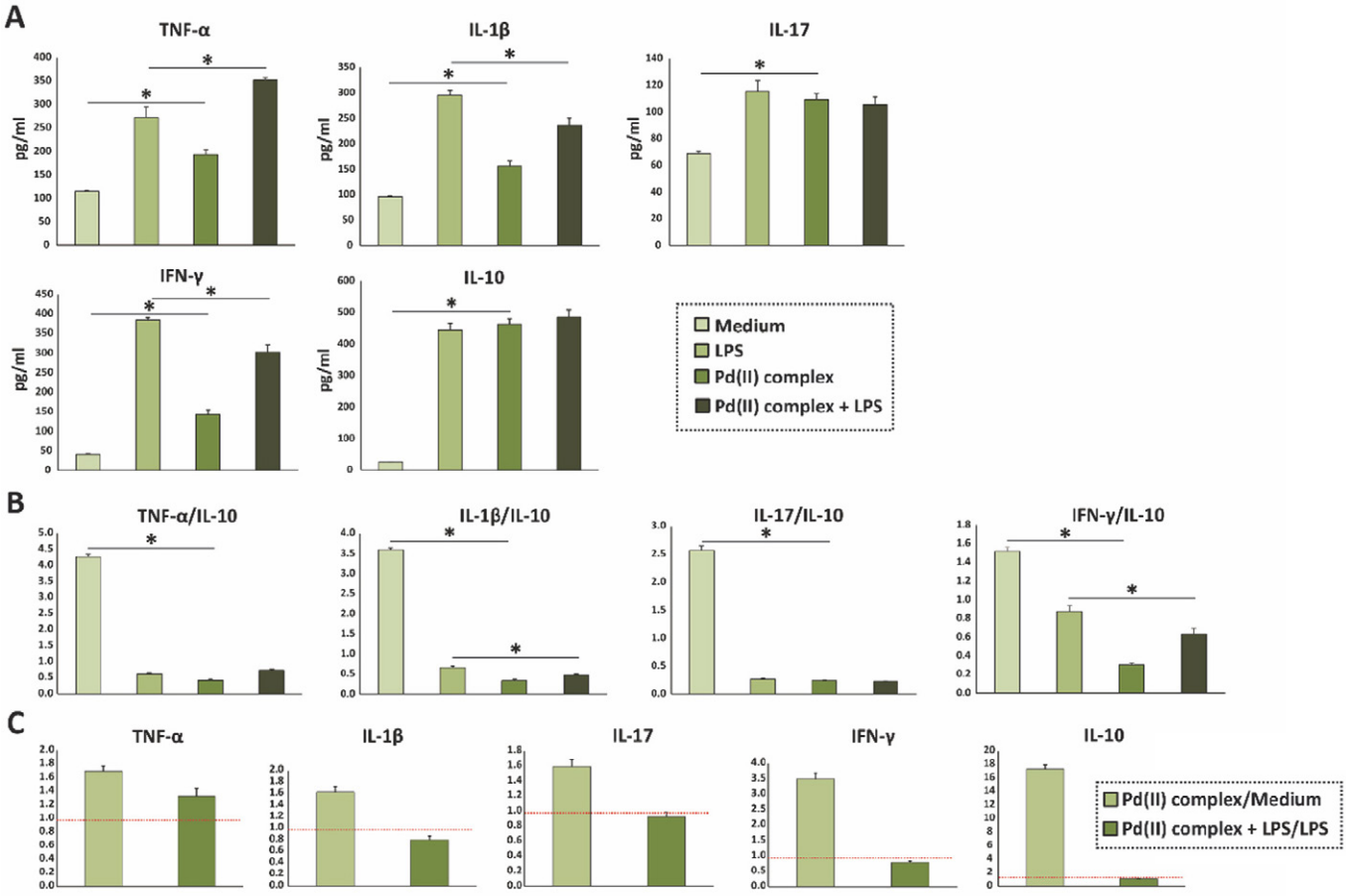


Figure 2: Effect of Pd(II) complex on cytokine production mediated by receptors of innate immunity cells (A) The concentration of cytokines produced by splenocytes incubated with medium only, LPS, Pd(II) complex or a combination of Pd(II) complex and LPS. The concentration of TNF-α, IL-1β, IL-17, IL-10 and IFN-γ were determined by ELISA. **(B)** Ratio of pro- and anti-inflammatory cytokine concentrations produced by splenocytes incubated with medium only, LPS, Pd(II) complex or a combination of Pd(II) complex and LPS. **(C)** Ratio of cytokine production - unstimulated (Pd(II)-complex/medium) and stimulated cells (Pd(II)-complex + LPS/LPS). The data are shown as mean ± SEM. Statistical significance was tested by the Mann-Whitney U test and Student's t-test, where appropriate. (*$p < 0.05$)

0.05) and IL-17 but without statistical significance compared to LPS incubated cells (Figure 2A). The same combination also led to an increase of TNF-α ($p < 0.05$) and IL-10 concentration but without statistical significance. When it comes to the ratios of contra-regulatory cytokines, LPS led to a significant decrease in the ratio of all measured pro-inflammatory and anti-inflammatory cytokines compared to untreated cells ($p < 0.05$) (Figure 2B). The Pd(II) complex also led to a decrease in the ratio TNF-α/IL-10 ($p < 0.05$), IL-1β/IL-10 ($p < 0.05$), IL-17/IL-10 ($p < 0.05$) and IFN-γ/IL-10 ($p < 0.05$) compared to untreated cells (Figure 2B). Cotreatment with Pd(II) complex and LPS led to a decrease in the ratio IL-1β/IL-10 ($p < 0.05$), IL-17/IL-10 (did not reach statistical significance) and IFN-γ/IL-10 ($p < 0.05$) compared with LPS-primed cells. The same combination led to a significant increase in the ratio of TNF-α/IL-10 ($p < 0.05$) (Figure 2B). Finally, analysis of the effect of the complex in relation to the activation status of target cells revealed increased ratio of TNF-α, IL-1β, IL-17, IFN-γ and IL-10 concentration in Pd(II)-complex treated against medium only was detected. The ratio of same cytokines concentrations in Pd(II)-complex+LPS treated against LPS only was significantly lower (Figure 2C).

Interestingly, Pd(II) complex showed the most intense effect on non-primed cells and also on anti-inflammatory IL-10 production, which increased it 16-fold, while it increased the production of pro-inflammatory cytokines by 2 to 4 times (Figure 2C). Inflammation and inflammatory responses are the synchronized stimulation of signaling pathways in immune cells that modulate the expression of inflammatory mediators. The major players in the inflammatory responses associated with diabetes, obesity, atherosclerosis, and neurodegenerative diseases are immune components of both the adaptive and innate immune systems: macrophages, lymphocytes, and the associated pro-inflammatory cytokines.[27–29] Among the immune cells, activated macrophages are the major cellular components that secrete not only pro-inflammatory cytokines, such as NO, TNF-α, IL-1β, and IL-6, but also numerous toxic substances.[30] Moreover, LPS, major components of the outer membrane of Gram-negative bacteria, are potent activators of the innate immune system via TLR4 expression on immune cells mainly of myeloid origin, including monocytes, macrophages and dendritic cells (DCs).[24–26] In line with these, our results implicate that the Pd(II) complex could be potent anti-inflammatory tool for combat with inflammation mediated with innate immune cells due to its effect on cytokines (Figure 2A, B).

4. Conclusion

Our results indicate the immunomodulatory capacity of the Pd(II) complex, which acts more intensely on unprimed cells of both innate and acquired immunity. Although it significantly affects the production of pro-inflammatory cytokines, its effect on the production of the anti-inflammatory cytokine IL-10 is many times greater. In conclusion, due to its immunomodulatory role, Pd(II) complex may be a good candidate for further testing in the field of medicinal chemistry. In addition to the potential antitumor effect, the Pd(II) complex also exhibits anti-inflammatory effects. This effect can be potentially useful in the therapy of numerous inflammatory diseases.

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Povzetek

Mnogi kompleksi so pokazali protitumorsko aktivnost, vključno s kompleksom bis(*S*-etil-2-tiosalicilat)paladij(II). Cilj te raziskave je preučiti potencialne imunomodulatorne učinke tega kompleksa na pridobljeno in prirojeno imunost *in vitro*. Učinek je bil ocenjen na podlagi ravni citokinov tumor nekrotičnega faktorja alfa (TNF-α), interlevkina (IL) 1β, interferona gama (IFN-γ), IL-17 in IL-10. Koncentracije citokinov so bile izmerjene z ELISA testom. Kompleks Pd(II) je povzročil zmanjšano izločanje večine pro-vnetnih citokinov. Učinki kompleksa so bili intenzivnejši v neaktiviranih celicah. Enak učinek je izkazan v celicah pridobljene in prirojene imunosti. Ti učinki kažejo, da je Pd(II) kompleks ne le potencialno protitumorno sredstvo, ampak tudi protivnetno sredstvo.