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Photo-induced anti-inflammatory activities of chloro substituted subphthalocyanines on the mammalian macrophage *in vitro*

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ABSTRACT

In this study, a series of subphthalocyanines (SubPcs) derivatives were synthesized to generate unique immunomodulatory molecules that can be activated through photo-induction. Immunomodulatory agents have a great potential in medicine to manipulate the immune system according to our needs and prevent disease symptoms. Inflammation is one of these symptoms and macrophages play a crucial role in the generation of inflammatory responses. Being able to control the activity of these agents through photo-induction enables the fine tuning on their activities in a location specific and non-invasive manner with possibly minor side effects. Mammalian macrophages' pro-inflammatory activity was examined in the presence of our compounds as well as LPS as a danger mimic. These compounds exerted photo-induced anti-inflammatory activities on the macrophages. Number of Cl atoms was a defining factor in their photo-induced anti-inflammatory immunomodulatory efficiencies.

1. Introduction

Regulation of the immune system by synthetically designed molecules has gathered attention due to its immense potential in medicine [1–14]. Being able to manipulate the immune response against a specific danger signal would enable us utilization from disease specific and personalized medicine rather than conventional therapies that lead to side effects [1–14]. These side effects are generated due to non-specificity of the drug molecules. Immunomodulatory molecules are designed to circumvent the non-specific activities of the anti-inflammatory molecules or adjuvants by fine tuning of the immune cells' reactions [1–14]. Moreover, their activity span cannot be controlled within the body. Therefore, new generation of carriers have been created to regulate the controlled release of the drug molecules in more of a tissue even cell type specific targeted fashion [15]. Another approach for controlled activity of the drug molecules is Photodynamic therapy (PDT) or photo-induced activation where a specific wavelength of light is used to activate the otherwise relatively dormant compounds [16,17]. Previous applications of PDT focus on the death of the cancerous cells or inflammatory cells of the immune system after the light exposure but in the photo-induced activation method; we do not aim to eliminate the cells by inducing their death. Instead, photo-induction aims to activate the dormant compound that would in turn alter and modify the activity of the targeted cells, in our case the immune system cells [16–19].

Macrophages are the main target of our studies due to their unique antigen presenting cell characteristics [20–30]. These cells are able to present the antigen to other immune system cells to further activate and direct the immune response against the danger associated antigens [20–30]. Moreover, macrophages produce a large scale of pro-inflammatory cytokines that can regulate the type and strength of the immune response [20–30]. These cells are mainly the part of the innate immune system that acts as the first line of the response against the invaders as well as injuries and trauma [20–30]. By interfering the function of a cell type that is heavily involved both at the initial stage of the immune response and also that can modulate the immune system cells at later stages present a great opportunity to develop immunomodulatory drug candidates. In this way, the function of the main cell type that can regulate the immune system is targeted. This approach would give more reliable information about the immunomodulatory capacity of the subphthalocyanine (SubPc) derivatives that were used in this study.

In a way we are aiming to immunomodulate the main modulatory cell type of the immune system. Macrophages produce TNF, IL6, IL1β, GMCSF, and IL12p40 as the pro-inflammatory cytokines to further activate and also regulate the other immune cells and generate a strong

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inflammatory response to eliminate the danger [20–30]. After elimination of the danger, inflammation is cleared out by immunosuppressive cytokines such as IL10 and TGFβ; so that the inflamed tissue can start the wound healing process and function properly [20–30]. In chronic inflammations or inflammatory disorders such as autoimmune diseases; the ongoing inflammation leads to the destruction of the tissue [1–14]. In those disease settings, the generation of anti-inflammatory immunomodulatory agents, that can regulate the immune cell activities by fine tuning, stands as the most vital and effective way to eradicate the inflammation [1–14]. Steroid based or non-steroid based strong immunosuppressive drugs lead to the side effects that can further exacerbate the patient's situation [1–14]. Moreover, their uncontrolled activity leads to more detrimental outcomes [1–14]. Therefore, photo inducible immunomodulatory molecules present a great potential to the field. Photo induction would enable localization of the drug activity as well as more control and regulation over the timing of the drug activation [15–19]. Fine tuning of the immune response according to the disease case would enable safer clearance of the inflammation and would pave the way for tissue regeneration [1–14].

Biological activities, including the immunomodulatory and anti-inflammatory activities, of the phthalocyanine and porphyrin derivatives were investigated by our group and others[31–35].

However, the aggregation of these compounds and their poor solubility in organic solvents limit their biomedical applications [36]. Unlike related Pcs, SubPcs are non-planar (cone shaped) aromatic compounds and thereof exhibit less aggregation tendency which makes them more soluble in many organic solvents [37]. The outstanding optical and electrical properties of SubPcs, such as intense absorption in the visible light region, make them strongly appealing multi functional components in the material science field [38]. SubPc derivatives have been extensively used as an electron donor or electron acceptor component in the photovoltaic devices [39]. These materials have extremely high power conversion efficiencies in the photovoltaic devices [39]. Indeed, these compounds are synthetically versatile and therefore their optoelectronic properties can be modulated by the introduction of an appropriate substituent in the axial and/or peripheral positions of the macrocycle [37]. More specifically, many SubPc derivatives have been used in a variety of donor − acceptor systems for the construction of the efficient artificial photosynthetic devices that can convert solar energy into the other forms (chemical, electricity, etc) of energy [41]. These features together with an intense absorption spectrum in the visible light range and high fluorescence quantum yield provide an additional potential for these materials to be used as sensitizers in biomedical applications especially in PDT and photo-induced drugs [42–45]. Recently, we obtained data supporting the PDT potential of SubPc derivatives [35]. However, the use of SubPc as a sensor in biological applications is not as common as those of the phthalocyanines and their immunomodulatory activities have not been investigated sufficiently. Previous studies suggest that the rate of halogenation can be a defining factor in the biological activities of the photosensitizers [19,35]. In our study, we aimed to delinate the effect of number of Cl substitution on either axial or peripheral position of the SubPc macrocylce and how this would change their photo-induced immunomodulatory capacities. In this regard, we synthesized four different SubPc derivatives. SubPc 1 was unsubstituted reference molecule. SubPc 2 contained six Cl atoms, while SubPc 3 had eight Cl atoms at the peripheral position. Moreover, there were Cl atoms at the axial positions of SubPc 2 and 3. In order to examine the effect of Cl atom at the axial position, we synthesized SubPc 4 which had phenoxy unit at axial position instead of Cl while keeping the eight Cl atoms at its peripheral position.

2. Materials and Methods

2.1. In vitro Cell activation studies

- Cell Culture: RAW 264.7 mouse macrophage cell line was purchased from ATCC and grown in Roswell Park Memorial Institute media (RPMI 1640) media with %10 fetal bovine serum, %1 antibiotics (100 μg/ml penicillin and 100 μg/ml streptomycin) and sodium pyruvate. 37 ^{0}C % 5 CO_2 incubator was used for the cell growth processes and experiments.

- Preparation of SubPCs: SubPc 1[46],2[47], 3[48] and 4[49] were prepared according to the previously described procedures in the literature. DMSO was used as their solvent to test their biological activities.

- SubPC and Lipopolysachharide (LPS) treatment of the mammalian macrophages: RAW 264.7 cells were used in 10^6 cells/well concentration in 1 ml fresh complete RPMI as described above in 24-well plates. Cells were rested overnight in 37 ^{0}C 5% CO_2 incubator before the experiments. 1ug/ml, 10ug/ml and 100ug/ml of SubPC derivatives were used on RAW 264.7 cells in the presence and absence of the LPS. 1 μl/ml of LPS (1 mg/mL, Enzo Life Sciences, Salmonella minnesota R595) concentration was used. 1ug/ml, 10ug/ml and 100ug/ml of SubPC derivatives and LPS treatment was conducted for 24 hours in 37 ^{0}C 5% incubator. Before starting the 24 hours incubation period appropriate sample plates were exposed to the Xenon light at specified time length (0, 1, 5 and 10 minutes). Afterwards supernatants of each well were collected and kept at -80^{0}C before ELISAs. Triplicates were set up for each experimental condition and these triplicate trials were repeated at least in four different independent experiments.

- Photo Induction: Xenon Light 300 Watt was used for the photo induction. 0, 1, 5 and 10 min time points were used as the light treatment periods. Compounds were added into the appropriate wells with overnight rested cells, then 0, 1, 5 and 10 minutes of Xenon light was applied to the appropriate plates. Afterwards the plates were put into the 37 ^{0}C 5% incubator for 24 hours.

- TNF, IL6 and IL1β ELISAs: TNF, IL6 and IL1β production was measured by using the enzyme-linked immunosorbent assay (ELISA). For each cytokine type manufacturer's instructions were followed by using the BD Biosciences, CA, USA ELISA kits.

- Cell counting and proliferation: Trypan Blue was used to count the dead and live cells and draw the cell viability after 24 hours.

2.2. Statistical analysis

GraphPad Prism Software version 5 was utilized for plotting the graphs and statistical analysis.

3. Results and Discussion

We prepared a series of SubPc derivatives decorated with different number of Cl atoms at the peripheral position (Fig. 1). Furthermore, we investigated their immunomodulatory activities on the mammalian macrophages especially by focusing on how the number of halogen substituents at the axial positions affected the activity of the SubPcs. In the previous studies, it was shown that halogenation of the photosensitizers increased their biological activities by enhancing the fluorescence and singlet oxygen quantum yields due to the heavy atom effect [40]. In the light of those results, we modified the axial position of the SubPcs to bear a bulkier and non-polar phenoxy group to compare it against the ones that have Cl in their axial positions (Fig. 1). In this study we also examined the effect of the photo induction on the activities of these SubPC derivatives. Photo induction property would enable us better control on their activities in the biological systems as well as in personalized medicine's *ex vivo* cell treatment phase [41].

These compounds were used in low micromolar levels. Non-cytotoxic concentrations were preferred for our studies (Figure ES1-4).

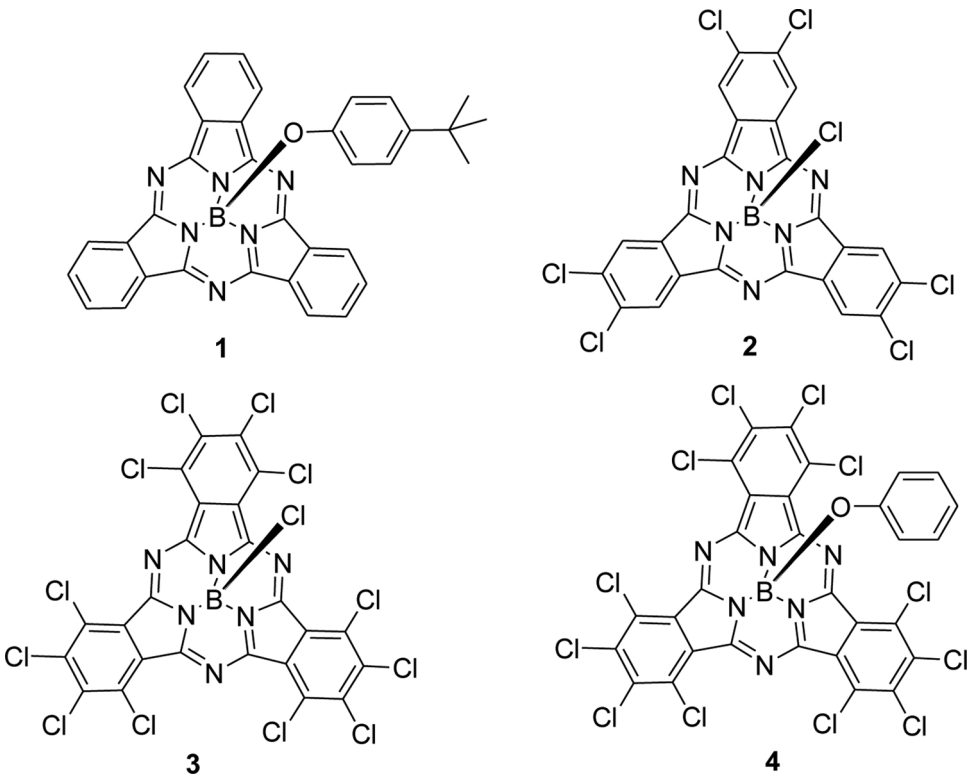

Fig. 1. Molecular structures of SubPc derivatives.

Photo-induced effect was examined by treating the samples with Xenon light (300 Watt) for 0 min, 1 min, 5 min. and 10 mins [42].

A well characterized RAW 264.7 mammalian macrophage cell line was used in our studies [18–28]. In negative control groups, only the DMSO solvent treated cells were used and in positive control groups 1 μg/mL LPS was used to stimulate the cells. After 24 hours, TNF and IL6 ELISAs were conducted to determine the differences in the pro-inflammatory cytokine production in the presence of different SubPc derivatives (Figure ES1-4). In order to test the immunostimulatory activity of the derivatives, the cells were treated in the absence of the danger mimic: LPS.

3.1. SubPc gained adjuvant potential by having phenoxy group at the axial position and the Xenon light treatment knocked this effect out

None of the derivatives except the high concentration (100 μg/mL) of SubPc **4 with phenoxy group at its axial position,** could stimulate the TNF production by the macrophages in the absence of a danger stimulus (Fig. 2 and Figure ES1-4). Strikingly, this effect was eliminated after the light treatment (Fig. 2 and Figure ES1-4). Moreover, SubPc **4** could not stimulate the IL6 production by the macrophages (Figure ES1-4). Therefore, it can differentially regulate the pro-inflammatory cytokine production by the macrophages. In cases where TNF production is required while excluding the IL6 production, this SubPc derivative would be a good candidate as an immunostimulator/adjuvant (Fig. 2).

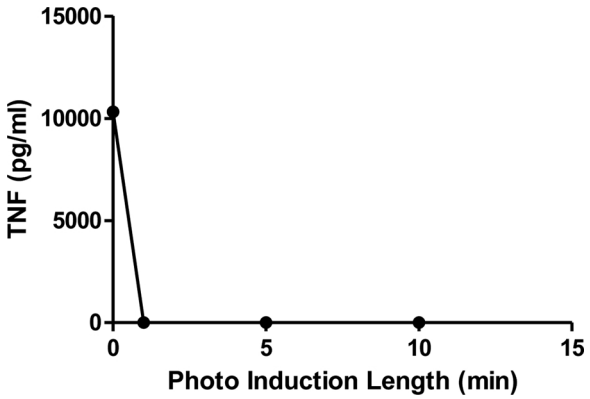

Fig. 2. TNF ELISA for the supernatants of RAW macrophage cells that were stimulated for 24 hours with 100 ug/ml of 4 in the absence of LPS. 0, 1, 5 and 10 minutes of Xenon light was applied to different sets of the samples to activate the compound. 1×10^6cells/ml cell concentration was used. SubPc **4** had adjuvant effect in the absence of photo-induction for the production of TNF. After photo-induction it loses the immunostimulatory activity completely.

3.2. SubPc derivatives gained a strong immunomodulatory potential upon Xenon light treatment

Immunomodulatory activities of the SubPc derivatives were tested in the presence of a danger stimulus, LPS (Figure ES1-4). Macrophages were treated with 1 μg/mL of LPS to get activated. The effect of the SubPcs on the macrophage activity was measured in the absence and presence of different periods of the light treatment and compared to the only LPS treated positive controls (Figure ES1-4). SubPc derivatives were mostly dormant and did not lead to a substantial change in the production of pro-inflammatory TNF and IL6 cytokines by the activated macrophages in the absence of light treatment (Figure ES1). With the photo-induction, these derivatives exerted differing anti-inflammatory activities by decreasing the TNF and IL6 production levels significantly and substantially compared to the positive control groups (Figure ES1-4). SubPc 3 had a mild intrinsic anti-inflammatory activity in the absence of the light treatment (Fig. 3). Increasing the length of the light treatment, lead to increases in the anti-inflammatory immunomodulatory activities of the SubPc derivatives (Fig. 3). Anti-inflammatory activities were more striking at the highest concentrations of the SubPcs (Figure ES1-4). These compounds were more effective in decreasing the TNF concentration; since it required lower doses of the SubPcs as well as shorter light treatment period to induce its production

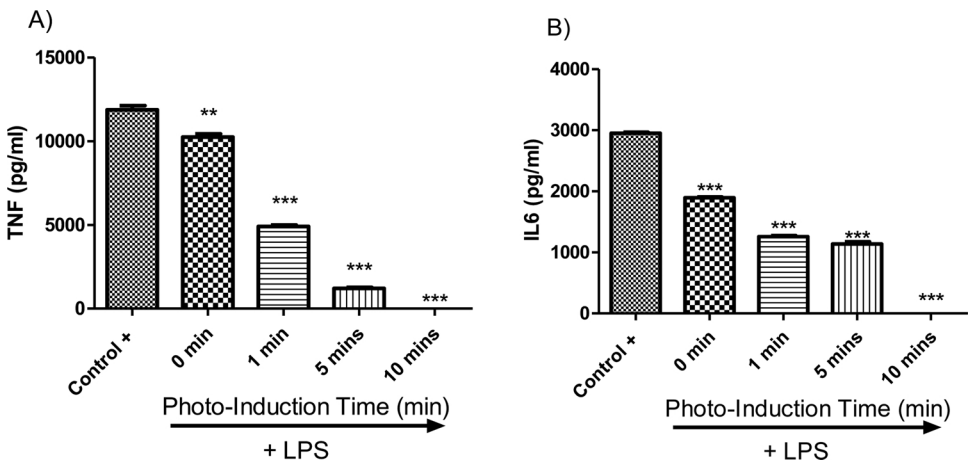

Fig. 3. Macrophages were treated with the SubPc **3** (100 μg/mL) in the presence of 1 μg/mL of LPS and compared to only LPS treated positive control group. Cells were stimulated for 24 hours with 100 ug/ml of 3 in the presence of LPS as a danger mimic. 0, 1, 5 and 10 minutes of Xenon light was applied to the different sets of the samples to activate the compound. 1×10^6cells/ml cell concentration was used. It exerted the highest anti-inflammatory activity by decreasing the TNF (A) and IL6 (B) production. Among the molecules that we tested, 3 was the most halogenated one. It's anti-inflammatory activity got more substantial by increasing the length of the light treatment.

Table 1
Photo inducible immunomodulatory activities (IA) of SubPc derivatives.

SubPc	IA	IA without Photo-induction	IA after Photo-induction
1	None	Yes	Yes
2	None	None	Yes
3	None	None	Yes
4	Yes	None	Yes

by the macrophages (Figure ES1-4). Whereas, longer period of light treatment and higher concentrations of the compounds, were required to induce the decrease in the IL6 production (Figure ES1-4).

3.3. The number of Cl ions at the axial position of SubPcs was a defining factor in their photo-induced immunomodulatory activities

The most potent anti-inflammatory SubPC derivative was the one with the highest number of Cl substitution (Figure ES1-4). Therefore, the number of Cl ions available in the environment lead to the changes in the immunomodulatory activities of the SubPcs. Having a phenoxy group at the axial position also lead to a change in the activity of the SubPC compared to the Cl substituted SubPcs (Figure ES1-4 and Table 1). Without the light treatment SubPc **4** had immunostimulatory/adjuvant activity on the macrophages and this effect was abrogated with the photo-induction, even after 1 min of exposure to the Xenon light (Fig. 2).

3.4. Bulkier, non-polar groups at the axial position of SubPcs decreased their photo-induced immunomodulatory activities

Moreover, SubPc **4** had a decreased anti-inflammatory activity on the macrophages compared to the other SubPcs. This suggests that having a bulkier, non-polar group at the axial position lead to a decreased activity. For all of the SubPcs at least 1 min of the photo induction was required to enable their anti-inflammatory activity, otherwise they were dormant and had no substantial effect on the production of TNF and IL6 cytokines by the LPS stimulated macrophages (Figure ES1-4, Tables 1 and 2). Increasing the light treatment period lead to an increase in the anti-inflammatory activities of SubPcs (Figure ES1-4). The higher number of Cl carrying SubPc **3** had stronger anti-inflammatory activity even with the shorter period of the light treatment (Fig. 3). Therefore, the number of Cl ions substituted to the SubPc axial position, determines the strength of their photo inducible immunomodulatory activities.

Table 2
Anti-inflammatory activity (a-IA) change of SubPcs according to the radiation time.

SubPc	a-IA without radiation	a-IA with 1 and 5 min radiation	a-IA with with 10-min radiation	Photo-inducible
1	Weak	Strong	Very Strong	Yes
2	None	Strong	Very Strong	Yes
3	None	Very Strong	Very Strong	Yes
4	None	Medium	Very Strong	Yes

4. Conclusions

SubPc derivatives with chloro substitution had strong immunomodulatory activities. They were dormant without the photo-induction but after the light treatment they gained an anti-inflammatory potential. This potential was stronger with longer exposure times to the Xenon light and with higher number of available Cl atoms at the axial position.

Having a bulkier phenoxy group at the axial position of the SubPc derivative lead to striking changes in its activity. This derivative (**4**) had adjuvant potential in the absence of the photo-induction (Figure ES1-4). Upon the light treatment, it had anti-inflammatory activity that was less effective than that of Cl bearing SubPc derivative (**3**) (Figure ES1-4 and Table 2). Due to the electron transfer and photosensitizer efficiencies of the SubPcs they have a great potential to be used as controlled (photo-inducible) anti-inflammatory immunomodulatory agents to fight against inflammatory disorders, including the autoimmune diseases. In this study, for the first time to our knowledge, we are presenting a detailed analysis of the unique SubPc derivatives with immunomodulatory potentials. More studies will be conducted to further delineate their mechanism of action on the immune cells as well as their *in vivo* efficacies.

Conflicts of interest

"There are no financial or non-financial conflicts to declare".

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pdpdt.2019.02.002.

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