Anti-inflammatory response of activated macrophages using lipid based formulation and its synergy with antioxidant toward the healing of inflammatory diseases

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(脂質を基盤とする製剤を用いた活性化マクロファージの抗炎症性応答と、炎症性疾患治療を志向した抗酸化剤との相乗効果)

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論　文　内　容　の　要　旨

Controlling inflammatory response is crucial to avoid the chronic inflammation which leads to severe diseases including neuroinflammation and allergic syndromes such as atopic dermatitis or ulcerative colitis. Macrophage plays a major role for controlling the inflammatory response in human immune system. Conversion of macrophage phenotype from pro-inflammatory to anti-inflammatory is important for the fundamental healing of such inflammatory diseases. The goal of this study was to design nanoparticles loaded simultaneously with both antioxidant and anti-inflammatory molecules targeting the phenotype of macrophages. Thus, we used a combination of α-tocopherol and phophatidylserine containing nanoparticles for resolving the inflammatory response of macrophages.

In chapter 2, I introduced α-tocopherol and phosphatidylserine (PS) containing liposomes (PST-liposomes) to inhibit inflammatory response of microglia, a residential macrophage of brain. PS is known to have anti-inflammatory effects on microglia, while α-tocopherol is an antioxidant, known to neutralize ROS. We found that both PS-containing liposomes (PS-liposomes) and PST-liposomes, as compared with phosphatidylcholine containing liposomes, significantly increased viability of hypoxia-treated microglia derived cell line. The PST-liposomes functioned better than the PS-liposomes and I attribute this superior effect to a synergy between PS and α-tocopherol. This synergic action of PST-liposomes was illustrated in their ability, when incubated with microglia, to reduce NO and pro-inflammatory cytokine (TNF-α) production and increase anti-inflammatory cytokine (TGF-β1) production. The improved viability of hypoxia-treated microglia when treated with PST-liposomes involved anti-inflammatory effects, including ROS neutralization, as well as induction of a microglial phenotypic change. This results suggest that PST-liposomes will represent a potential therapeutic approach for reducing ischemic injury in brain.

In chapter 3, a phosphatidylserine (PS)-coated microparticles was prepared instead of liposome and tried to apply to AD mouse model for achieving the modulation of the macrophage phenotype to an anti-inflammatory state. Here I prepared poly (D, L-lactate) microparticle coated with PS on the outside shell. I confirmed the cellular uptake of the PS-coated microparticle, which leads to the significant downregulation of the inflammatory cytokine production. In the

mouse model of AD, the PS-coated microparticle showed significant reduction in development of AD symptoms comparing with the mice treated with the PC-coated microparticle with subcutaneous injection.

In chapter 4, preparation of potential anti-oxidative and inflammatory property-bearing biodegradable polymer/lipid hybrid nanoparticle (PLNP) containing both α-tocopherol and phosphatidylserine was reported. Then their consequent up-regulation of anti-oxidative and anti-inflammatory response was investigated in activated mouse peritoneal macrophages.These two components showed a clear synergistic anti-inflammatory and anti-oxidative effects compared with those having only α-tocopherol or PS. Compared with PC-, PCT- or PS-PLNP, the PST-PLNP significantly increased the viability of macrophages. Our data also demonstrated that PCT-, PS- and PST-PLNP significantly suppress the production of NO and inflammatory cytokine, with highest effect showed by PST-PLNP when those cells are stimulated. The PST-PLNP performed better than the PCT- and PS-PLNP and I attribute this highest effect resulted from a synergy between α-tocopherol and PS. The PST-PLNP also showed their anti-inflammatory effect by the production of anti-inflammatory cytokine TGF-β1 in activated macrophages. The potential anti-inflammatory and anti-oxidative effects of the PST-PLNP indicates the phenotypic modulation of the macrophages. Therefore, this α-tocopherol and phosphatidylserine containing polymer-lipid hybrid nanoparticle could be a potential drug carrier and effective approach for healing the chronic inflammatory diseases such as ulcerative colitis.

In chapter 5, the contribution of this research was summeraized.