Spermidine activates mitochondrial trifunctional protein and improves antitumor immunity in mice(Abstract_要旨)

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論文題目	Spermidine activates mitochondrial trifunctional protein and improves antitumor immunity in mice （スペルミジン はマウスにおいてMitochondrial trifunctional protein複合体を活性化させ抗腫瘍免疫を増強する）		

（論文内容の要旨）

The function of immune system of mammals gradually declines with age. Many factors contribute to this phenomenon including a decrease in the output and diversity of the antigenic repertoire of T cells caused by thymus involution, changes in the cellular metabolism caused by inflammation, and defective proliferative, differentiation or survival capacities of the immune cells. Spermidine (SPD), a biogenic polyamine is reported to decrease with age, and SPD supplementation was shown to improve or delay several age-related pathologies, including those of the immune system. SPD is proposed to function in the rejuvenation of immune system, enhance autophagy, derive translational activity and mitochondrial metabolism. SPD supplementation was previously shown to enhance the anti-tumor immunity in animal models. However, it remains largely unknown how SPD deficiency relates to the T cell immune suppression induced by ageing.

As CD8+ T cells are key players in tumor immunity, it is of utmost importance to understand how aging would impact the metabolic and functional characteristics of CD8+T cells. The aim was to characterize the CD8+ T cell populations changes induced by SPD supplementation in aged mice and explore the molecular mechanisms for the SPD action in CD8+ T cell.

Both the total and free intracellular concentrations of SPD were reduced in CD8+T cells from aged mice compared to those in young mice. Bioenergetically, aged CD8+ T cells showed impaired mitochondrial activity with lower oxygen consumption rate, ATP production and fatty acid oxidation (FAO) activity, compared to young CD8+ T cells. SPD supplementation enhanced the anti-tumor activity of PD-1 blockade immunotherapy in aged mice and young mice. In addition, SPD supplementation proved to also be effective in young mice with tumors unresponsive to single anti-PD-L1 antibody therapy.

In vivo, SPD and anti-PD-L1 antibody combination treatment enhanced the effector function of CD8+ T cells such as proliferation, cytokine production and mitochondrial ATP production.

In vitro, SPD effectively enhanced mitochondrial functions of CD8+ T cells within one hour of stimulation, suggesting the possibility of direct SPD binding to mitochondria-related proteins. Biochemical analysis identified SPD binding to mitochondrial tri-functional protein (MTP), which is the central enzyme of fatty acid □-oxidation. MTP subunits alpha and beta both could bind to SPD. MTP synthesized and purified from E. coli bound to SPD with strong affinity (Kd = 0.1 □M). Biochemical assays showed that SPD allosterically enhanced the enzymatic activities of MTP. Also, T cell specific deletion of the MTP alpha subunit abolished enhancement of PD-1 blockade immunotherapy by SPD, indicating MTP requirement for SPD-dependent T cell activation.

The results of this study describe a novel mechanism of SPD by which FAO is enhanced directly through the binding and activation of MTP. SPD supplementation enhances the FAO activity, boosts the mitochondrial activities and cytotoxic functions of CD8+ T cells. These new insights into the properties of SPD could facilitate development of strategies to prevent and improve outcomes of age-related immune pathologies and, overcome unresponsiveness to PD-1 blockade therapy in cancers regardless of age.

（論文審査の結果の要旨）

老化によりT細胞免疫が低下することは、高齢者にてCOVID19ワクチンが効きにくいことや、がんの発症率が上がること等によりよく知られている。しかし老化による免疫不全メカニズムには未解明な点が多く残されている。生体内ポリアミンであるスペルミジン（spermidine: SPD）は細胞の生存、増殖、ミトコンドリアの機能維持に必須である。そのため、細胞内には豊富に含まれているが、加齢とともにその生体内濃度は低下する。SPDはその抗老化作用が注目されているが、その多機能性ゆえ、作用機序には不明が多く残されている。申請者は、老化とともにSPDがT細胞においても減少し、エネルギー産生や脂肪酸酸化等のミトコンドリア機能の低下の原因になっていることを明らかにした。老化マウスではミトコンドリア機能不全のためT細胞機能が低下し、PD-1阻害抗体治療が無効になっていた。しかし、SPDを補充（併用）することで、老化個体においてもがんに対する免疫力が回復した。SPDは試験管内実験にて短時間でミトコンドリアによる酸素呼吸を上昇させた。生化学的解析によりSPDはミトコンドリアに存在する脂肪酸酸化を担う酵素（mitochondrial trifunctional protein）に直接結合し、その酵素活性を上昇させることが明らかになった。これらの結果は、老化個体にて免疫力が低下する一因を説明する発見であり、また今後がん免疫治療や自己免疫等の免疫関連疾患の機序解明・治療法開発の礎となる研究成果である。

したがって、本論文は博士（医学）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、令和　5年　1月　6日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。