| 京都大学 | 博士（医科学） | 氏　名 | Chong Yee Kien |
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| 論文題目 | Cyclin J–CDK complexes limit innate immune responses by reducing proinflammatory changes in macrophage metabolism<br>（Cyclin J-CDK 複合体はマクロファージの代謝を介し炎症性変化を抑制することで自然免疫応答を調節する） | | |

（論文内容の要旨）


The activation of macrophages is controlled by the dynamic metabolic changes induced by extracellular stimuli such as Toll-like receptor (TLR) ligands and viral infection, as well as environmental changes like hypoxia. Particularly, glycolysis activation as well as mitochondrial reactive oxygen species (ROS) production are known to promote inflammatory responses in macrophages. Despite elaborate studies on innate immune metabolism, the regulatory mechanism of macrophage metabolic changes is not fully understood.

The aim of this study was to investigate the function of Cyclins in macrophage innate immune responses. Using publicly available database of macrophage activation, an atypical cyclin, called cyclin J, was identified to exhibit unusual inducibility by TLR ligands such as LPS and Type I Interferon. Cyclin J was then demonstrated to function as an unconventional repressor of TLR-induced inflammatory responses in macrophages using both overexpression and genetic depletion approaches. In-depth analyses revealed that Cyclin J affects metabolic activity of macrophage through suppression of glycolysis processes, shown by the depletion in gene expression encoded for glycolytic genes, production of HIF-1α, and reduction in glycolysis process. Cyclin J was further identified to affect mitochondrial oxidative phosphorylation with notable changes in mitochondrial fitness, including reduced membrane potential and capability of ROS production upon activation. Mechanistically, Cyclin J associates with Cyclin-dependent kinases (CDKs) and the interaction is required for its immune-regulatory function in macrophages. As the Cyclin/CDK complex triggers phosphorylation on a set of specific substrates, phosphoproteomic analysis was then performed and a unique set of proteins phosphorylated by the Cyclin J/CDK complex was discovered in macrophages. Further analyses uncovered that Cyclin J targets immuno-metabolic signaling in macrophages through FoxK1 and Drp1, respectively. Cyclin J/CDK-mediated phosphorylation of FoxK1 resulted in impaired glycolytic gene transcription by the impairment of its nuclear localization. On the other hand, Drp1 phosphorylation by Cyclin J/CDK led to mitochondrial fission and suppression of ROS production. Overall, Cyclin J coordinately controls metabolism and thereby suppresses inflammatory responses in macrophages. To address the functional roles of Cyclin J in macrophages *in vivo*, sub-lethal dose of LPS was injected into mice to mimic septic shock.  The results showed that myeloid-specific Cyclin J-deficient mice experienced higher fatality with heightened serum pro-inflammatory cytokine profile compared with control mice. On the other hand, mice were systemically infected with *S. aureus* infection and showed that myeloid-specific Cyclin J-deficient mice were protected from succumb to fatality with lower bacterial burden in multiple organs together with elevated cytokine production. Beyond acute infection model, the role of Cyclin J was examined using cancer model using both xenograft and colitis-associated cancer models, in which Cyclin J could mediate tumor progression through affecting the behavior of tumor associated macrophages, with elevation of pro-tumoral and pro-inflammatory characters with the change in metabolic status such as glycolysis. In summary, this study provides a new perspective of Cyclin J-CDK-mediated immuno-regulation by identifying a novel role of Cyclin J in controlling macrophage function via immuno-metabolism. Our evidence showed that global inhibition or activation of CDKs can affect cellular functions such as cell cycling and transcription broadly, in addition to the immune regulation. Therefore, this new finding provides a different perspective for the establishment of novel therapeutic approaches, in which developing small molecules targeting Cyclin expression in modulating CDK activity of macrophage are promising in controlling both infectious diseases and tumor progression in future.


（論文審査の結果の要旨）

マクロファージは、感染に対する炎症応答や組織修復、がん免疫などに重要である。トル様受容体(TLR)を介して病原体を認識したマクロファージは、炎症に関わる多くの遺伝子を発現するが、その過程で代謝のダイナミックな変化がおこる。Cyclin ファミリーは進化的に保存され、サイクリン依存性キナーゼ (CDK)と結合して細胞周期を調節するが、その炎症制御における役割は不明であった。

本研究ではまず、マクロファージにおいて TLR 刺激により発現誘導される分子として Cyclin J を同定した。マクロファージで発現する Cyclin J は、TLR 刺激に対する解糖系の活性化とミトコンドリアの活性酸素種発現を抑制し、炎症性サイトカインの遺伝子やタンパク質発現を負に制御する事を明らかにした。その分子機構として、Cyclin J が CDK と結合し、CDK による標的タンパク質のリン酸化を調節すること、そのリン酸化標的として FoxK1 や Drp1 があり、そのリン酸化がそれぞれ解糖系とミトコンドリア制御に関わることを見出した。また、マクロファージに発現する Cyclin J は、マウスの個体レベルで、敗血症性ショックを抑制する役割を持つと共に、腫瘍随伴マクロファージを制御しがん免疫応答に必要である事も明らかにした。

以上の研究は、マクロファージの代謝を通じた感染防御やがん免疫応答の制御機構解明に寄与するところが多い。

したがって、本論文は博士（医科学）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　4 年　5 月　31 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。

要旨公開可能日：　　年　　月　　日　以降