

Title	Regnase-1 Regulates Maturation and Tumor Surveillance of Natural Killer Cells Through Its Endonuclease Activity
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Osaka University

Abstract of Thesis

Name (Xin Sun)

Title

Regnase-1 Regulates Maturation and Tumor Surveillance of Natural Killer Cells Through Its Endonuclease Activity

(RNA分解酵素Regnase-1によるNK細胞の成熟および抗腫瘍活性の制御)

Abstract of Thesis

Post-transcriptional regulation plays an essential role in orchestrating immune system. Many immune response related mRNAs with short half-lives are conserved *cis*-element, such as adenylate-uridylylate (AU)-rich elements (AREs) and stem-loop (SL) structured in their 3' untranslated regions (UTRs).

Regnase-1 (also known as Zc3h12a, Mcpip1) is a novel RNase protein with endonuclease activity that acts as a negative regulator for immune system . Regnase-1 destabilizes immune related target mRNA via the stem-loop structure in the its 3'utr. Recent accumulating reports showed that Regnase-1 serves as a crucial regulator in maintenance of immune homeostasis and degradation of inflammatory mRNAs.

Natural killer (NK) cells are essential anti-tumor effector lymphocytes of the innate immune system. NK cell possess the ability to control a broad spectrum of tumor cells by controlling tumor growth and metastasis. Upon activation , NK cells directly lysis target cells by secreting perforins, granzymes and multiple cytokines, such as IFN- γ , TNF- α .

Deficiency of Regnase-1 in T cells leads to the enhance T cell activation and massive production of cytokines. However, the intrinsic interaction between Regnase-1 and NK remains unexplored. By using a NK cell-specific Regnase-1 conditional knockout mice, here I found that number of NK cell from Regnase-1 deficient mice (Reg-1 ^{Δ NK}) was severely reduced and Regnase-1 is required during NK cell maturation stage. Furthermore, Regnase-1 ^{Δ NK} mice showed strong anti-tumor activity compared with Regnase-1^{fl/fl} mice and depletion of NK cells from Regnase-1 ^{Δ NK} mice attenuated anti-tumor activity. Collectively, my results reveal the essential role of Regnase-1 in NK cell differentiation and Regnase-1, as a potential checkpoint of NK cells can be a promising anti-cancer therapeutic strategy.

論文審査の結果の要旨及び担当者

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<p>RNA分解酵素Regnase-1は、免疫反応に関連する複数の標的遺伝子のメッセンジャーRNA (mRNA) を特異的に分解することによって、免疫細胞によって引き起こされる炎症反応や免疫応答を制御する。本研究ではナチュラルキラー (NK) 細胞による細胞障害活性に対するRegnase-1の機能的役割を明らかにすることを目的とした。まず、NK細胞特異的にRegnase-1遺伝子を欠損したマウスでは、NK細胞の産生するサイトカインや細胞溶解性蛋白質の産生量が著しく向上し、<i>in vitro</i>及び<i>in vivo</i>の条件でRegnase-1遺伝子欠損マウス由来NK細胞は野生型と比較して腫瘍細胞に対して強い細胞障害活性を示し、腫瘍の転移を著しく抑制した。これらの研究結果はRegnase-1遺伝子の新たな機能的役割を解明する重要な成果であり、学位授与に値するものと認める。</p>	