



Title	The ectoenzyme E-NPP3 negatively regulates ATP-dependent chronic allergic responses by basophils and mast cells
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論 文 内 容 の 要 旨
Synopsis of Thesis

氏 名 Name	蔡仕翰
論文題名 Title	The ectoenzyme E-NPP3 negatively regulates ATP-dependent chronic allergic responses by basophils and mast cells (E-NPP3は好塩基球と肥満細胞によるATP依存性の慢性アレルギー炎症を負に制御する)
論文内容の要旨	
〔目的(Purpose)〕	
<p>Basophils and mast cells have critical roles in immediate and chronic allergic responses through FcεRI crosslinking-mediated inflammatory mediators and cytokines release. However, it remains unclear how the chronic allergic inflammation is regulated. Several studies demonstrated that nucleotide-converting ectoenzymes regulate immune responses through nucleotide hydrolysis. E-NPP3 (CD203c), which is a member of ecto-nucleotide pyrophosphatase-phosphodiesterase (E-NPP) family, has been identified to be the trustful and useful biomarker of basophils activation in diagnosis of allergic diseases. However, the function of E-NPP3 (CD203c) remains undetermined despite its high expression in activated basophils. Extracellular adenosine 5'-triphosphate (ATP), which is released by activated immune cells and damaged cells during inflammation, has been recognized as a danger signal. Several evidences indicated that extracellular ATP activates mast cells via the purinoreceptor P2X7. However, it remains unclear how ATP-dependent mast cell responses are regulated. Furthermore, it should also be elucidated whether extracellular ATP influence on basophils, which share several immunological functions with mast cells. In this study, we characterized the roles of extracellular ATP and E-NPP3 in basophils- and mast cell-related chronic allergic responses.</p>	
〔方法ならびに成績(Methods/Results)〕	
<p>We first showed that surface expression of E-NPP3 was rapidly induced on mouse bone marrow-derived basophils and mast cells after FcεRI crosslinking. Next, we analyzed the physiological function of E-NPP3 (CD203c) using <i>Enpp3^{-/-}</i> mice. <i>Enpp3^{-/-}</i> mice had increased numbers of basophils in the blood and spleen and mast cells in the intestines with elevated serum ATP levels. Moreover, <i>Enpp3^{-/-}</i> mice were susceptible to chronic allergic pathologies mediated by basophils and mast cells, such as chronic allergic skin inflammation, experimental oral allergen-induced diarrhea, and experimental chronic asthma. Treatment with ATP antagonists ameliorated the allergic responses observed in <i>Enpp3^{-/-}</i> mice. ATP secretion was induced by FcεRI crosslinking from basophils and mast cells, and ATP, in turn, activated both cells. In addition, ATP clearance was impaired in <i>Enpp3^{-/-}</i> basophils and mast cells, which resulted in strong activation of <i>Enpp3^{-/-}</i> basophils and mast cells via activation of ERK1/2. Non-hydrolyzable ATP activated WT basophils and mast cells to comparable levels observed in <i>Enpp3^{-/-}</i> cells. Treatment of P2X7 antagonists and introduction of the <i>P2rx7</i> deficiency into <i>Enpp3^{-/-}</i> mice reduced ATP-dependent responses by basophils and mast cells and decreased the number of basophils and mast cells in vivo.</p>	
〔総括(Conclusion)〕	
<p>Extracellular ATP was induced by FcεRI crosslinking strongly activated basophils and mast cells via P2X7, which mediated chronic phases of allergic responses. E-NPP3, which was rapidly induced on basophils and mast cells after FcεRI crosslinking, suppresses ATP-mediated overactivation of basophil and mast cells through ATP hydrolysis. In the absence of E-NPP3, ATP clearance activity was impaired. Thus, extracellular ATP level was increased in serum of <i>Enpp3^{-/-}</i> mice, leading to development of enhanced basophils- and mast cells-dependent chronic allergic inflammations. However, introduction of the <i>P2rx7</i> deficiency into <i>Enpp3^{-/-}</i> mice resulted in the decreased activity of basophils and mast cells. This study demonstrated that P2X7 mediates the ATP-dependent overactivation of basophils and mast cells in an ATP autocrine manner and E-NPP3, which is rapidly induced on activated basophils and mast cells, plays a negative regulatory role in basophils- and mast cells-mediated chronic allergic inflammations via ATP degradation.</p>	

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

近年患者数が増加の一途をたどる喘息やアトピーなどのアレルギー疾患は、マスト細胞・好塩基球によって引き起こされることが知られている。しかし、マスト細胞・好塩基球の活性が普段どのように制御されているかについては不明な点が多かった。

本研究にて、アレルギーで活性化された好塩基球で発現が高くなる酵素 E-NPP3 (CD203c) を欠損したマウスを作成したところ、マスト細胞・好塩基球が活性化状態になり、皮膚アレルギー、食物アレルギー、喘息が悪化することを見出した。また、E-NPP3 はアデノシン三リン酸 (ATP) を分解する膜型酵素であり、ATP のアレルギーへの関与を解析したところ、アレルギーで活性化されたマスト細胞・好塩基球は ATP を分泌し、分泌された ATP がマスト細胞・好塩基球自身をさらに活性化、アレルギーを悪化させることが明らかになった。そして、E-NPP3 が、活性化されたマスト細胞・好塩基球で速やかに発現し、ATP によるアレルギー反応を抑制することも明らかになった。

以上の知見は、マスト細胞・好塩基球による慢性アレルギー反応の病態を理解するうえで極めて重要な知見であり、今後、ATP、E-NPP3 を標的とした喘息や皮膚アレルギーへの新たな治療法の開発が期待されるもので、学位の授与に値すると思われる。