Form 3

Abstract of Thesis

Name （Parajuli Gyanu）	
Title	Arid5a augments tryptophan metabolism and chemokine expression to promote the immune evasion of mesenchymal tumor subtypes. （Arid5a はトリプトファン代謝とケモカインの発現を増幅することによって腫瘍の免疫からの回避を促進する）

Abstract of Thesis

The acquisition of mesenchymal traits in immunologically cold tumors leads to immune evasion. However, the underlying molecular mechanisms that link tumor immune evasiveness and mesenchymal phenotypes remain unclear. In this study, I found that the expression levels of AT-rich interaction domain-containing protein 5a (Arid5a), an RNA-binding protein, is substantially increased in mesenchymal tumor subtypes. The deletion of Arid5a in tumor cell lines enhanced antitumor immunity in immunocompetent mice but not in immunodeficient mice, highlighting the role of Arid5a in immune evasion. Furthermore, an Arid5a-deficient tumor microenvironment was shown to have robust antitumor immunity, as manifested by the suppressed infiltration of granulocytic myeloid-derived suppressor cells and regulatory T-cells, whereas infiltrated T-lymphocytes were more cytotoxic and less exhausted. Mechanistically, Arid5a stabilized *Ido1* and *Ccl2* mRNAs and augmented their expression, resulting in enhanced tryptophan catabolism and an immunosuppressive tumor microenvironment. Furthermore, Arid5a expression was substantially increased in mesenchymal subtypes of pancreatic ductal adenocarcinoma (PDAC) and colorectal cancers (CRC), and Arid5a promoted TGF-β-induced and IL-6-induced epithelial-mesenchymal transition and acquisition of invasiveness in PDAC. Thus, my findings unraveled a novel role of Arid5a as a genetic driver of the immune evasion of mesenchymal tumors. My data expands the role of Arid5a beyond inflammatory diseases, and suggest Arid5a as a promising target for the treatment of immunotolerant malignant tumors.

様式７

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

癌細胞が免疫の働きを回避して増殖する機構に関して、Arid5A というRNA結合分子がトリプトファン代謝とケモカインの発現を促進することが関与するという新しいメカニズムを見出した。この結果は Cancer Immunology Journal に発表され高い評価をうけている。よって、博士の学位を授与するに値するものと認める。