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Prevention of Lung Carcinogenesis by Suppressing Pathogenic CD4 T Cells

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Chronic inflammation is increasingly recognized as an important factor that contributes to the development of a wide range of malignancies, including lung cancer. We recently found that Th17 cells, a type of immune cell, is critical to inflammation. Th17 cells and their signature cytokine, interleukin-17 (IL-17), have been detected in various human cancers, but their function in tumor development remained unclear. Using genetically modified mice that develop a lung adenocarcinoma whose pathophysiology resembles that of the human disease, we demonstrated that IL-17 plays a critical pathogenic role in lung cancer development. Therefore, the mutagenesis-driven early inflammatory process in tumor is critical to lung cancer progression, and understanding the mechanisms underlying these actions will substantially advance our knowledge of cancer development and potentially lead to improved treatment strategies.

In the proposed project, we will delineate the developmental pathways of inflammatory Th17 cells, which promote tumorigenesis, and those of immunosuppressive regulatory T cells (Tregs), which induce the immune system to disregard tumorigenesis. We will adapt transgenic mice to express the pathogenic cytokine IL-17 or the lineage-determining factor Foxp3, which will enable us to track and isolate Th17 cells or Tregs in a mouse model of oncogene-driven spontaneous lung cancer. Th17 cells derived from the lung adenocarcinoma of this model will be subjected to RNA sequencing to identify the molecules that enable Th17 cells to potentiate tumor progression. In addition, because T cells are known to recognize self-antigens and mutated antigens in the tumor microenvironment, we will employ high-throughput sequencing technology to identify the antigens required for Th17 cell induction. Given that pathogenic T cells promote tumor development, we also propose to use a mouse model of lung adenocarcinoma to test specific T-cell inhibitors that have been investigated in clinical trials of other malignancies or autoimmune diseases. The therapeutic agents we propose to test are an immune check point blockage anti–programmed cell death 1 antibody (for immune checkpoint blockage), and an anti–IL-17 antibody (for cytokine blockage), and phosphoinositide 3 kinase δ inhibitor (for targeting activation pathway of T cells). We hypothesize that these treatments will inhibit Th17 cells and Tregs, thereby suppressing inflammation and restoring the immune system’s ability to prevent tumor growth. Upon completion of the proposed work, we will have a better understanding of currently available cancer therapies that target immune cells, and we will use this new knowledge to design therapeutic agents that are tailored to inhibit tumor growth according to the status of immune response during tumor progression.
### 15. SUBJECT TERMS

None listed.

### 16. SECURITY CLASSIFICATION OF:

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### 17. LIMITATION OF ABSTRACT

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### 18. NUMBER OF PAGES

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### 19a. NAME OF RESPONSIBLE PERSON

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### 19b. TELEPHONE NUMBER (include area code)

None listed.
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1. **INTRODUCTION:**

Our proposed research is to understand adaptive immune response that is shaped by oncogene activation using animal model of early-stage non-small cell lung cancer. Our previous study demonstrated CD4 helper T cell producing Interelukin-17 (Th17) cells are critical for early lung tumor growth. While it is relatively well known how Th17 cells develop during autoimmune diseases or infections, little is known how these cells develop upon oncogene activation. Thus, our aim is to delineate molecular pathways governing protumorigenic Th17 cells and test therapeutic agents to harness pathogenic CD4 T cells. Completion of the proposed aims will provide advanced understanding on how pathogenic CD4 T cells develop in response to oncogene activation in lung and evaluate appropriate therapeutic agents to reduce tumor growth using oncogene induced model of lung adenocarcinoma.

2. **KEYWORDS:**

Inflammation, IL-17, Th17 cells, regulatory T cells, oncogene, lung adenocarcinoma, Kras

3. **ACCOMPLISHMENTS:**

   - **What were the major goals of the project?**

Specific Aim 1: Identify the cellular and molecular mechanisms responsible for establishing and maintaining pathogenic CD4 T helper 17 cells in an animal model of oncogene-driven lung adenocarcinoma. Milestone(s) Achieved: identification of antigen, molecular characteristics, and cytokine requirement of Th17 cells

Specific Aim 2: Determine the way in which the coordinated generation of Tregs and pathogenic Th17 cells is achieved upon oncogene activation and dissect the functional contribution of a Treg subset Milestone(s) Achieved: Understand the regulatory T cells developed upon oncogene activation

Specific Aim 3: Assess the ability of therapeutic agents to harness pathogenic CD4 T cells in a model of oncogene-driven lung adenocarcinoma. Milestone(s) Achieved: Identify the effectiveness of immunomodulatory drugs and anti-inflammatory agents to reduce tumor

   - **What was accomplished under these goals?**

Major activities during this year is described below with specific aims and major results/key outcomes.

**Aim 1:** Identify the cellular and molecular mechanisms responsible for establishing and maintaining pathogenic CD4 Th17 cells in an animal model of oncogene-driven lung adenocarcinoma.

1.1. *Identify the molecular requirement of Th17 cell development in genetically deficient mice lacking Th17-polarizing molecules.*

Our preliminary results showed that the pathways governing the development of lung tumor–infiltrated infiltrating Th17 cells were microbiota–independent, whereas those governing the development of colonic Th17 cells were heavily dependent on microbiota (Fig.1).
Given the unique characteristics of tumor-infiltrating Th17 cells and that tumorigenic condition do not result in autoimmunity, we sought to identify the fate of Th17 cells in CCSP\textsuperscript{Cre}/K-ras\textsuperscript{G12D} mice. Using sensitive fate-tracking reporter mice that permanently mark IL-17F–expressing cells with yellow fluorescent protein (YFP; IL17\textsuperscript{Cre}/Rosa26\textsuperscript{eYFP} mice), we found a stable population of YFP+ cells similar to innate IL-17–producing cells (e.g., γδ T cells) during acute infection (Fig.2), which is in sharp contrast to the chronic inflammation observed in experimental autoimmune encephalomyelitis or colitis.

1.2. Compare the molecular signatures of Th17 cells from isolated from lung adenocarcinoma with autoimmune Th17 cells

In our preliminary result, we showed Th17 cells from CCSP\textsuperscript{Cre}/K-ras\textsuperscript{G12D} mice do not deviate toward Th17/Th1 cells observed in other chronic inflammatory condition. Therefore, we propose to determine whether oncogenic events induce a distinctive set of protumorigenic Th17 cells. For this purpose, we further analyzed CCSP\textsuperscript{Cre}/K-ras\textsuperscript{G12D} tumor infiltrated CD4 T cells for cytokines other than prototypical cytokine IL-17. For instance, IL-22 has been shown to mediate protumorigenic function via activating STAT3 or stemness of tumor cells [1]. It is not known the function of IL-22 in lung cancer. To detect IL-22 in CC-LR mice first, we isolated mononuclear fraction of tumor lung and cultured with IL-1 and IL-23 overnight before adding PMA and Ionomycin for restimulation. Since the detection of IL-22 by intracellular staining was relatively weak and technically difficult possibly due to transient or monoallelic expression, we used IL-1 and IL-23 to enhance the detection of IL-22 by intracellular staining. Normal BALF did not have any measurable T cells while LRCC BALF showed enhance IL-22
positive cells. Control lung showed low level of IL-22, which is mostly γδ T cells, which was also shown by IL-22 reporter mice [2]. In CC-LR mice, IL-22 producing cells were increased and confined to Thy1 positive fraction. Approximately, half of IL-22 producing cells were TCRβ-positive CD4 T cells. Remaining IL-22 producing cells were mostly γδ T cells. Although IL-22 producing CD3− NKp46+ ILC3 are reported stage I/II NSCL cancers [3] and these cells are enriched in tissues such as colon, we did not see any presence of CD3− NKp46+ producing IL-22. We found IL-22 is expressed along with IL-17 in not only Th17 cells but also γδ T cells (Fig.3).

1.3. Identify the TCRβ clonal diversity of Th17 cells isolated from lung adenocarcinoma using next-generation sequencing to determine whether Th17 cells are generated in an antigen-specific manner.

We will isolate a pure Th17 cell population from tumor lung of IL-17FRFP CCSPcre/K-rasG12D mice as described in Fig 2. Since percentage of RFP positive cells are relatively low, we are currently in the step of enriching this population of cells. In addition, we found IL-17F positive cells diverge from IL-17A positive cells. Therefore, we obtained IL-17A reporter mice from Jackson laboratory and we are in process of breeding this strain with CCSPcre/K-rasG12D mice for more accurate representation of Th17 cells.

Aim 2: Determine the way in which the coordinated generation of Tregs and pathogenic Th17 cells is achieved upon oncogene activation and dissect the functional contribution of a Treg subset.

2.1. Determine whether Tregs promotes Th17 cells during tumorigenesis by short-term in vivo depletion and in vitro co-culture.

To understand better the characteristics of Tregs developed upon oncogene activation and local cues driven by lung microenvironment, we examined phenotype of Tregs in relevant to activation markers. Tregs isolated in lungs of LR-CC mice expressed well-described activation markers such as CD25, OX40 and PD-1. We also found CD39, CCR6 and CD103 expression (Fig. 4). This analysis will further provide molecular markers that can be used for short-term in vivo depletion.
2.2. Determine the role of RORγt+Foxp3+ Tregs in tumor progression by reconstituting bone marrow from RORγtffe/Foxp3cre mice in CCSPcre/K-rasG12D mice.

We proposed in this aim to create bone marrow chimeric mice by reconstituting bone marrow cells from wild type or RORγtffe/Foxp3cre mice in irradiated CCSPcre/K-rasG12D mice. RORγtffe/Foxp3cre mice is currently available in our colony. The CCSPcre/K-rasG12D mice was irradiated at age 6 weeks, and bone marrow reconstitution were completed. The chimeric mice will be evaluated for lung adenocarcinoma incidence at age 14 weeks. We recently completed ontology and biological function of RORγt+ Foxp3+ in autoimmune diseases (manuscript in revision) (Fig. 5 and Fig. 6). Our observation of RORγt+ Foxp3+ revealed that these cells are 1) it is Helio+, indicating thymic derived, not inducible, and 2) this is a highly suppressive Treg subpopulation.

Fig. 5 RORγT Tregs express ICOS and CCR6 and are highly proliferative. Seven days after MOG/CFA immunization, RORγT expression in each CD4+Foxp3+ subsets in dLNs was analyzed after gating based on ICOS and CCR6 expression. Ki-67 expression in RORSymbol+CCR6+ (Solid) or RORSymbol-CCR6- (Dashed) cells was analyzed.
Aim 3: Assess the ability of therapeutic agents to harness pathogenic CD4 T cells in a model of oncogene-driven lung adenocarcinoma.

3.1. Assess the ability of an anti–IL-17 antibody in combination with an anti–PD-1 antibody to suppress ongoing inflammation and restore the immunosuppressive environment.

Our primary results demonstrated that the expression of PD-1 in T cells and that of PD-L1 in tumor-infiltrating macrophages were increased in lung adenocarcinoma–bearing mice. However, we did not observe Kras mutated tumor cells or normal lung epithelium after tumor induction promoted PD-L1 expression (data not shown). We attempted PD-1/PD-L1 blockade in lung adenocarcinoma–bearing mice and found that treatment with an anti–PD-1 antibody alone did not affect tumor growth significantly, which has also been observed in two other recent studies that used the spontaneously arising animal cancer model. Therefore, we focus on aim 3.1. to see inhibition of Th17 cells would be more effective strategy rather than IL-17 and anti-PD-1 antibody treatment as we proposed.

3.2. Assess the ability of the kinase inhibitor (PI3K p110δ inhibitor) to suppress Th17 cells and Tregs.

We proposed to test p110δ in this aim to see if the treatment effectively reduce lung tumor by suppressing the generation of Th17 cells and Tregs simultaneously. In this study, we proposed to use PI-3065, a commercially available agent that has been tested in a K-ras mutation–driven pancreatic cancer model as well as in a transplantable solid tumor model. We administered PI-3065 (75 mg/kg once daily) or vehicle (0.5% methylcellulose with 0.2% Tween 80) to CCSPcre/K-rasG12D mice by oral gavage for 3 weeks. Results indicated that PI3Kδ inhibitors were not effective in inhibition of Th17 cells and Tregs. We think low turnover rate of Th17 cells may cause inefficient targeting by PI3Kδ inhibitors [4].
Since PI3K p110δ inhibitor was not successful inhibiting Th17 cells and Tregs, we evaluated several other known Th17 cell inhibitors. In the past, we have shown ursolic acid has been tested in our laboratory using the autoimmune disease model. Since the target organ in the previous study was CNS tissues in the previous study, we tested this agent using allergic asthma model where Th17 cells are generated in lung and play pathogenic function. Ursolic acid treatment efficiently suppressed Th17 cell responses in lung and reduced allergic inflammation (manuscript in revision) (Fig. 8).

![Graph showing lung weight of 14 weeks old CCSPcre/K-rasG12D mice treated with vehicle or PI3Kd inhibitor daily for three weeks. To examine whether Tregs and Th17 cells were suppressive by PI3Kd inhibitor, total lung including tumors were subjected for RNA isolation. RTPCR result of Foxp3, IL-17 and IFNg indicated similar level of these cytokine expression upon the treatment. Dot indicate the individual mice for the study.]

**Fig. 7 Lung weight of 14 weeks old CCSPcre/K-rasG12D mice treated with vehicle or PI3Kd inhibitor daily for three weeks.**

**Fig. 8 An RORγt inhibitor, ursolic acid suppresses both Th2- and Th17-mediated allergic inflammation in the airway.** Wild type mice were intranasally challenged with PAO/Ova on days 0, 2, 4, 6 for prevention mode (Fig. 3, A-D) or days 0, 2, 4, 6, 12 for therapeutic mode (Fig. 3, E-H). Ursolic acid was treated intraperitoneally on days 0, 2, 4, 6 for prevention mode and days 6, 8, 10, 12 for therapeutic mode, respectively. 24 h after the last challenge, mice were sacrificed and asthmatic phenotypes were analyzed. A and E, Frequency of BAL lymphocytes producing IFNγ, IL-4/5 and IL-17. B and F, Absolute number of BAL lymphocytes producing IFNγ, IL-4/5 and IL-17. C and G, Absolute number of total, macrophages, eosinophils, neutrophils and lymphocytes in BAL fluid. The graph shows means ± sem. *P < 0.05, **P < 0.01, ***P < 0.001. ns, Not significant. UA, ursolic acid. mac, macrophages. eo, eosinophils. neu, neutrophils. lym, lymphocytes.

- What opportunities for training and professional development has the project provided?

This grant is supporting PI to further develop her professional commitment to the research subject of lung cancer and immune response. With progress made in aim 2, PI further investigated subsets of Tregs in other inflammatory disease and found a unique regulatory pathway determining RORγt by
STAT3 in Treg cells. This observation led PI to apply NIH grant in autoimmunity and Treg and R21 was granted this year. Also, part of the aim 1 on IL-22 work is being incorporated into a manuscript with PI’s long-term collaboration in MD Anderson Cancer Center with Dr. Moghaddam. PI also formed a new collaboration with the department of interventional radiology in liver cancer with Dr. Avritscher to investigate the role of immune cells in hepatocellular carcinoma. PI will expand her research work into immune response in liver cancer, specifically on Th17 cells and Treg. This grant also allowed to have a new post-doctoral fellow to start to work on this project which she can learn basic immune response which occurs during tumorigenesis and develop appropriate skill sets and knowledge to solve scientific questions presented here and cancer immunology in broader aspects.

- **How were the results disseminated to communities of interest?**

Two manuscripts which are relevant to this proposal and partially addressed questions posed on specific aim 2 and specific aim 3 of this proposal are currently in revision process. Once these two studies are published, the results will be disseminated to scientific communities by presenting these work in conferences and internal (MD Anderson Cancer Center) and external seminars.

- **What do you plan to do during the next reporting period to accomplish the goals?**

**Aim 1:** Following up on those observations from Year 1, we plan to use the animals that are deficient of genes known to be critical for the generation of Th17 cells in autoimmune diseases. We will determine TGF-β and STAT3 are required to generate Th17 cells during oncogenesis. We indicated in SOW the phenotypic analysis of these animals will be examined in Year 2 since crossing these animals and reconstitution of bone marrow chimera requires 6 months to 1 year. Additional experiment will perform is to use TGF-β neutralizing antibody and STAT3 inhibitor to CCSPcre/K-rasG12D animals. We think this protocol will be complementary for the conclusion drawn by bone marrow reconstitution of TGF-β/CD4cre and STAT3/CD4cre mice. This aim also includes the molecular signature of Th17 cells and T cell receptor β (TCRβ) clonal diversity of Th17 cells from CCSPcre/K-rasG12D animals. For this purpose, IL-17F reporter cells from CCSPcre/K-rasG12D has been sorted and will accumulate sufficient number of cells for sequencing in Year 2. As we have observed diversion of Th17 cells producing IL-17F vs IL-17A in CCSPcre/K-rasG12D, we plan to examine IL-17A reporter mice in CCSPcre/K-rasG12D background.

**Aim 2:** Based on the Year 1 progress, we identified unique signature of Treg cells in the tumor lungs of CCSPcre/K-rasG12D mice. Using antagonizing antibody against these molecules, we plan to deplete or block local Tregs infiltrated in tumor. Although local Treg depletion may not be effectively diminish the tumor progression, the discovery made in this goal will help combination therapy which the anti-tumor immunity pathway is not redundant. Since the analysis of RORyt+ Foxp3+ Tregs indicated that these cells are thymic-derived suppressive Treg subpopulation, we are going to make bone marrow chimera of RORyt/fox3cre to CCSPcre/K-rasG12D to address the function of RORyt+ Foxp3+ Tregs in CCSPcre/K-rasG12D mice in Year 2.

**Aim 3:** Our progress in Year 1 indicated PD-1 antibody therapy alone or a kinase inhibitor is not efficient for reducing tumor growth. As we identified an alternative therapy, ursofic acid, is efficient in suppressing Th17 cells in lung, we will use this treatment regime and dose for CCSPcre/K-rasG12D mice. Also, during the progress of Aim 2, we identified distinctive signature of Treg that are unique to
CCSP<sup>cre</sup>/K-ras<sup>G12D</sup>. Since the current therapeutic approaches to deplete Tregs are either not efficient or cause autoimmune disease due to systemic depletion of Tregs, we will use Treg specific antibody to depleted tumor infiltrated Tregs. Tregs in tumor have been described to promote Th17 cells as well in colorectal cancer. Considering concomitant increase in Treg and Th17 cells in CCSP<sup>cre</sup>/K-ras<sup>G12D</sup>, depletion of Tregs could lead not only enhanced anti-tumor immunity but suppress inflammation by suppressing Th17 cells localizing to tumor lung. We will test this hypothesis in Year 2.

4. **IMPACT:**
   - **What was the impact on the development of the principal discipline(s) of the project?**

   We identified the cellular source of IL-22, an inflammatory cytokine, in the animal model of lung cancer. Our results support the significance of γδ T cells in lung that are promoted by oncogene to produce IL-17 and IL-22 in addition to conventional CD4 T cells. This result is incorporated into a study which demonstrates a protumorigenic function of IL-22 in lung cancer (a manuscript in preparation). We also examined immunosuppressive regulatory CD4 T cell in cellular details. One of accomplishments is to demonstrate various activation markers of tumor infiltrated Tregs, which can be useful for localized Treg suppression in the following study. Also, we examined the ontogeny of RORγt Treg, a thymic derived and potent immunosuppressive subset of Tregs (a revised manuscript submitted). This provided a basis to examine its function in oncogene-driven lung cancer model. Lastly, we examined various pathways to harness immunosuppressive pathways in lung cancer model. Due to the lack of effect by PD-1 antibody alone or PI3Kδ inhibitor, we tested other agents that can suppress pathogenic CD4 T cells in lung. Ursolic acid was efficient in suppressing RORγt in lung during inflammation (a manuscript in revision). This prompted us to examine the validity of ursolic acid in lung cancer animal model.

   - **What was the impact on other disciplines?**

   We consider the immune response developed during oncogene-activated lung cancer model is not confined observation in animals nor lung cancer. While human cancer develop with more mutations and shaped by dynamic tumor microenvironment, the progress made using an animal model of lung cancer could be applied to other cancer type as well. It is well known that large tumor accompanying metastasis is difficult to cure. Since the current animal model used in this study represents immune response early in lung cancer, exploration of interventional methods using this model pose advantages for effective cancer treatment focusing on early stage of cancer.

   - **What was the impact on technology transfer?** *Nothing to Report*
   - **What was the impact on society beyond science and technology?** *Nothing to Report*

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:
   - **Changes in approach and reasons for change**

   All of specific aims remain the same.
Actual or anticipated problems or delays and actions or plans to resolve them

We plan to complete the project in Year 2.

Changes that had a significant impact on expenditures Nothing to Report
Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents Nothing to Report
Significant changes in use or care of human subjects Nothing to Report
Significant changes in use or care of vertebrate animals Nothing to Report
Significant changes in use of biohazards and/or select agents Nothing to Report

6. PRODUCTS:
   Publications, conference papers, and presentations

   - Journal publications.

       Concomitant suppression of Th2 and Th17 cell responses in allergic asthma by targeting RORγt. Na H, Lim H, Kim BK, Kim S.-H., Chang Y.-S., Dong C, Chang SH*, Chung Y* (* co-corresponding author) (revised version is submitted to Journal of Allergy and Clinical Immunology, acknowledgement of federal support; yes)


   - Books or other non-periodical, one-time publications. Nothing to Report
   - Other publications, conference papers, and presentations. Nothing to Report

Website(s) or other Internet site(s) Nothing to Report
Technologies or techniques Nothing to Report
Inventions, patent applications, and/or licenses Nothing to Report
Other Products Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

   - Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).
If information is unchanged from a previous submission, provide the name only and indicate "no change."

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<td>Dr. Chang has supervised the overall projects and performed work in the area of Treg cellular phenotype analysis, tested inhibitor of RORgt in vivo model, analyze the functional aspects of RORgt Foxp3 Tregs in lung cancer model.</td>
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<td>Dr. Wang has started on April 2017 and led work in the area of Treg mediated cellular functions in lung cancer model. She participated in projects to elucidate the development of Tregs in lung cancer.</td>
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- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - A new grant has been awarded to PI since the last reporting period. New project does not overlap with this grant and efforts of the PI to this grant remains the same.

- **What other organizations were involved as partners?** *Nothing to Report*

7. **SPECIAL REPORTING REQUIREMENTS**
   - **COLLABORATIVE AWARDS:**
   - **QUAD CHARTS:**
8. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT RENUMBER PAGES IN THE APPENDICES.**

References