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ORAL ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Role of the S1P Signaling Pathway in the Pathogenesis of Angioimmunoblastic T-Cell Lymphoma

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Peripheral T cell lymphomas (PTCLs) are a group of aggressive lymphoid malignancies originating from mature T cells. Angioimmunoblastic T-cell lymphomas (AITL) represent 20% to 30% of all PTCL diagnoses and are associated with autoimmune features, poor response to chemotherapy, and dismal prognosis. Molecular profiling of AITL has identified T-follicular helper (TFH) cells as the cell of origin of AITL, while mutational analysis has identified frequent alterations in epigenetic regulators (*TET2, DNMT3A*, and *IDH2*) and elements of the TCR pathway as drivers of AITL transformation. Our group identified the highly recurrent *RHOA G17V* mutation as a defining hallmark of AITL and other T-cell lymphomas of TFH-cell origin (Palomero *et al.*, 2014). Using a novel conditional knockin mouse model, we demonstrated that expression of *Rhoa* G17V in CD4+ T-cells induces TFH cell specification and promotes AITL lymphomagenesis in the context of loss of *Tet2* (Cortes *et al.*, 2018).
Recently, we have identified that *Rhoa* G17V regulates the expression of the sphingosine-1-phosphate (S1P) receptor 1 (S1PR1) one of the five members of the receptor family of S1P, which plays an essential role in immune response and lymphocyte trafficking. During thymic T-cell development, expression of *Rhoa* G17V in CD4+ cells inhibited S1PR1 downregulation after the double positive stage leading to altered positive selection, reduced CD4+ single positive cell numbers and premature thymic egress of autorreactive T-cells which results in the development of systemic inflammation and autoimmunity. In our *Tet2* $^{-/-}$ *RHOA G17V* AITL tumor model, constitutive activation of S1P receptors supported activation of the STAT3 and NFkB pathway and enhanced migration of malignant cells to peripheral organs. Mechanistically, expression of *Rhoa G17V* in mature CD4+ T-cells impaired re-phosphorylation of the Ezrin-Radoxin-Moesin (ERM) complex independently of ROCK signaling and led to the activation and increased migration of CD4+ T-cells. Importantly, blockade of S1PR1 signaling by fingolimod induced anti-tumor activity in *Tet2* $^{-/-}$ *RHOA G17V* lymphoma-bearing mice in vivo with significant reductions in tumor burden associated with increased apoptosis and decreased STAT3 phosphorylation. Furthermore, analysis of a panel of primary tumors from AITL patients using a multiplexed staining panel and PhenoImager platform revealed significantly higher S1PR1 expression in AITL tumor cells than normal TFH cells from benign reactive lymph nodes. Our findings highlight the role of S1P signaling pathway in the pathogenesis of *RHOA G17V*-driven AITLs and the potential therapeutic benefit of targeting this pathway.

Disclosures Rodriguez Cortes: *Regeneron Pharmaceuticals, Inc.:* Current Employment. **Rabadan:** *AimedBio:* Membership on an entity's Board of Directors or advisory committees; *Arquimea Research:* Consultancy; *Genotwin:* Membership on an entity's Board of Directors or advisory committees. **Ferrando:** *Regeneron Pharmaceuticals, Inc.:* Current Employment. **Palomero:** *Kura Onclology:* Research Funding.

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