PROGRESS REPORT
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T cells (T lymphocytes) are the primary effectors of the adaptive immune system. Each individual T cell expresses a T-cell receptor (TCR) specific for a particular antigen peptide presented by major histocompatibility complex (MHC) proteins; collectively, the T-cell population triggers immune responses against a wide variety of foreign antigens and plays an essential role in protecting the bodies from pathogens. On the other hand, T cells do not normally elicit immune responses against self-antigens. This highly diverse, specific, and self-tolerant TCR repertoire is primarily formed through selection processes in the thymus.

The thymus is an organ essential for T cell maturation and selection. T-precursor cells originating from the bone marrow differentiate into CD4/CD8 double-positive (DP) thymocytes in the thymic cortex. Through rearrangement of the TCR gene loci, they express TCRs, enabling them to recognize self-peptide/MHC presented on cortical thymic epithelial cells (cTECs). DP cells that receive moderate TCR signals undergo positive selection and differentiate into CD4 single-positive (CD4SP) or CD8SP thymocytes. DP cells expressing TCRs that strongly recognize self-peptide/MHC receive strong TCR signals and are induced to die by programmed cell death. This process is referred to as negative selection. SP thymocytes migrate to the thymic medulla, where they are further screened for self-reactivity. Strong interaction between TCRs and self-peptide/MHC displayed by medullary antigen-presenting cells such as medullary thymic epithelial cells (mTECs) induces negative selection of self-reactive SP thymocytes, allowing only non-self-reactive cells to survive as mature T cells. Some self-reactive CD4SP thymocytes differentiate into regulatory T cells (Tregs), which suppress immune responses against self in peripheral tissues. The ability of T cells to attack non-self while sparing self is acquired through these selection mechanisms in the thymus, which is regulated by complex cell-cell interactions and molecular signaling.

We have studied the molecular mechanisms of T cell repertoire selection in the thymus from the perspective of the thymic microenvironment. Thymic stromal cells, which architect the thymic microenvironment, possess complex mechanisms for presenting appropriate self-peptides according to the differentiation stage of developing thymocytes. Furthermore, the maturation of thymic stromal cells is also induced in response to thymocyte development, establishing an interdependent relationship between the two. Moreover, the relationship between thymocytes and thymic stromal cells fluctuate upon thymic involution caused by aging or stresses. Understanding the mechanisms underlying T cell development, repertoire selection, and their fluctuations during thymic involution and regeneration will greatly contribute to solving medical challenges such as treating autoimmune diseases and enhancing vaccine responses.

In April 2024, I joined this institute as a Professor of the Division of Molecular Pathology and opened new laboratory. In May, we accepted two master's degree graduate students, and in July, Dr. Ryunosuke Muro joined as an Assistant Professor. By the end of 2024, we completed the setup of the laboratory equipment and research infrastructure for studying T cell development in the thymus.

Positive selection in the thymic cortex

The thymic cortex is the site where T-cell repertoire formation begins. cTECs possess unique protein degradation mechanisms mediated by cTEC-specific proteasome, lysosomal proteases, and high autophagy activity. These mechanisms enable the presentation of a unique set of self-peptides via MHC class I or class II on cTECs, efficiently inducing positive selection to generate diverse repertoire of T cells.

We have studied the mechanism of positive selection mediated by cTEC-specific proteasome, termed thymoproteasome. The catalytic subunit β5t (encoded by the PSMB11 gene), a key component of thymoproteasome, is essential for positive selection of CD8 T cells (Nitta et al, ***Immunity*** 2010). In addition, the genetic variations of human *PSMB11* gene affect the MHC class I-bound peptide repertoire in the thymus and positive selection of CD8 T cells (Nitta et al, ***Sci Immunol*** 2017). One of the *PSMB11* polymorphisms, G49S, detected in the Japanese population at a high frequency, was associated with a higher risk of Sjögren's syndrome. These results suggested that, in addition to the MHC haplotype, genetic variations of proteasome influence T cell repertoire selection and susceptibility to autoimmunity. We are currently investigating the mechanism how positive selection by thymoproteasome generates diverse T-cell repertoire, focusing on the structure of TCR. We are also examining the effects of the PSMB11 G49S polymorphism found in the Japanese population on virus infection and vaccine responses.

Collaborator:

Ryunosuke Muro

Negative selection in the thymic medulla

In the thymic medulla, mTECs express a wide variety of proteins that are intrinsically expressed only in peripheral tissues, such as insulin (pancreas-specific) and CRP (liver-specific). These tissue-restricted antigens (TRAs) are processed within mTECs and then presented on MHC molecules as short self-peptides, that enable the deletion of self-reactive SP thymocytes and their differentiation into Tregs.

Approximately half of TRA gene expression in mTECs is controlled by unique transcription mechanisms mediated by the nuclear protein Aire. Recently we reported that transcript splicing is also essential for the production of TRAs in mTECs. Protein arginine methylation is an evolutionarily conserved posttranslational modification involved in various biological processes such as mRNA processing. We found that protein arginine methyltransferase 5 (Prmt5), a key enzyme for the symmetric dimethylation of arginine residues, is highly expressed in Aire-expressing mTECs (Muro et al, ***J Clin Invest*** 2024). In TECs, Prmt5 targets the proteins involved in spliceosome factors, which are essential for the pre-mRNA splicing of a large number of genes including Aire and a broad range of TRA genes. Loss of Prmt5 in TECs results in the development of organ-specific autoimmunity, indicating that Prmt5 is required for the induction of central tolerance. These findings highlight the critical roles of optimized transcript splicing in facilitating the expression of a broad repertoire of self-antigens in mTECs.

The development of mTECs and the expression of Aire require signaling via the receptor RANK (receptor activator of nuclear factor kappa B), expressed on mTECs. In the thymus, RANK ligand (RANKL) is predominantly expressed on CD4SP thymocytes. RANK signaling is negatively regulated by osteoprotegerin (OPG), a decoy receptor for RANK that is mainly produced by mTECs.

However, the physiological significance of this feedback regulatory mechanism remains unclear.

We investigated the immunological significance of OPG in T cell development. Mice with conditional knockout of OPG in TECs (OPGcKO) exhibited an approximately fourfold increase in mature mTECs compared to controls, whereas the expression pattern of representative self-antigens in mTECs remained largely unchanged. These mice showed significantly lower diversity of the TCR repertoire, which was associated with a decreased number of self-reactive T cells and foreign antigen-reactive T cells. Consistent with this, OPGcKO mice showed reduced autoimmune responses, diminished reactivity to gut commensal microbiota, and attenuated vaccine responses. These results suggest that an excess of self-antigens relative to immature T cells in the thymic medulla leads to the elimination of foreign antigen-reactive T cells, possibly due to cross-reactivity of self-antigens with foreign antigen-reactive T-cell receptors. The immunological significance of the OPG-mediated fine-tuning of mTEC development is likely to optimize the amount of self-peptides in response to the number of newly generated T cells to preserve as many foreign peptide-reactive T cells as possible, while still allowing the generation of a certain number of self-reactive T cells (Mino et al, submitted).

Thymic medulla also contains stromal cell types other than mTECs, including fibroblasts, endothelial cells, and vascular mural cells. Characterization and functional studies on non-TEC stromal cells have lagged behind compared to TECs. In recent years, the development of multicolor flow cytometry and single-cell and spatial transcriptomics has rapidly elucidated the nature and function of non-TEC stromal cells at the molecular level. We have focused on non-TEC stromal cells, advancing our understanding of these cells through the identification of molecular markers and gene expression profiles (Nitta et al, ***Nat Immunol*** 2020; Nitta et al, ***Immunol Rev*** 2021). We have demonstrated that thymic medullary fibroblasts contribute to the induction of immune self-tolerance by expressing self-antigens, supporting mTEC development, and controlling the migration of SP thymocytes. Our research will continue to focus on the role of medullary fibroblasts and other non-TEC stromal cells in controlling medullary microenvironment and T-cell selection both in the steady state and during thymic involution.

Collaborators:

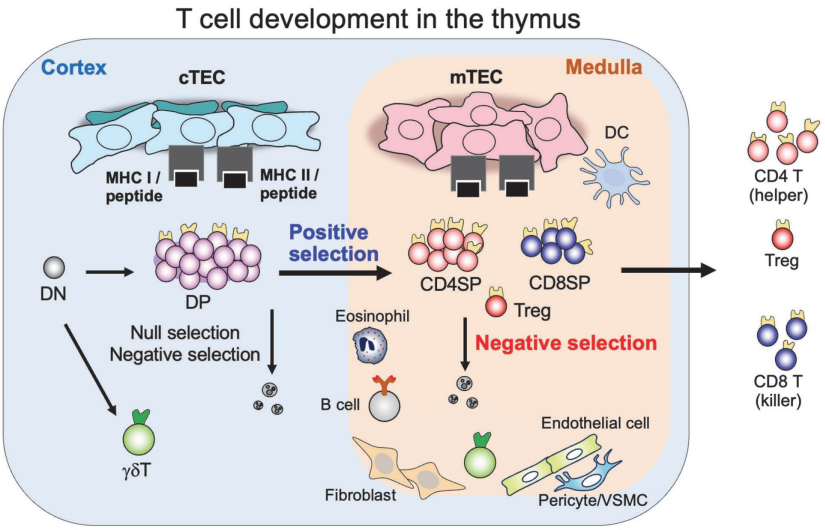
Keisuke Toda, Ryunosuke Muro

Molecular mechanisms regulating thymic involution and regeneration

The thymus is the first organ affected by aging. Its T cell-producing function peaks in infancy or early childhood. After adolescence, it undergoes progressive atrophy (thymic involution), with structural and functional changes including TEC disorganization, adipogenesis, and reduced in T cell development. Recent studies show that the thymus continues to produce T cells, albeit in small numbers, even in the elderly, but the significance of these age-specific T cells remains unclear.

Apart from age-related involution, the thymus undergoes acute involution in response to infection, pregnancy, stresses, radiation, and cytotoxic chemicals. These factors induce apoptosis of DP thymocytes, leading to rapid reduction in thymus size and decline of the T cell population. Unlike age-related involution, acute thymic involution is reversible: the thymus size and function return to normal within weeks after insult removal. Recent thymus research has focused on how stromal cells and hematopoietic cells in the thymus contribute to these dynamic changes.

Using acute thymic involution models induced by lipopolysaccharide or dexamethasone, we found a significant reduction in mature mTECs and medullary fibroblasts, both of which



How is T-cell repertoire selection regulated in the thymus?
How is it associated with thymic involution and regeneration?

express tissue-restricted antigens for clonal deletion of self-reactive T cells. These results indicate that acute thymic involution temporarily disrupt the medullary microenvironment crucial for T cell repertoire selection. Furthermore, it was found that gene expression in medullary fibroblasts dramatically changed during the acute thymic involution, including the induction of the expression of OPG, a factor that suppresses mTEC development. We are investigating whether and how these stromal cell-cell interactions contribute to changes in the medullary microenvironment and T cell selection during thymic involution.

Eosinophils are innate immune cells abundantly present the thymus, and recent studies have reported their contribution to thymic regeneration following acute involution. We characterized the gene expression and differentiation mechanism of thymic eosinophils in mice. Thymic eosinophils showed a distinct gene expression profile compared with other organ-resident eosinophils, and its unique gene expression required the differentiation of immature DP thymocytes. The number of thymic eosinophils was controlled by mTECs likely via chemokine expression. These results demonstrate that thymic eosinophils are qualitatively and quantitatively regulated by developing thymocytes and mTECs, respectively, suggesting that thymic eosinophils are a distinct, thymus-specific cell subset, induced by interactions with thymic cells (Ota et al, ***Int Immunol*** 2024). We are currently using mice deficient in thymic eosinophils to investigate their role and mechanism in thymic regeneration.

Collaborators:

Hiromasa Matsumoto, Ryunosuke Muro

Publications

Takeshi Nitta, Ryunosuke Muro

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Division of Molecular Pathology

Akihiko Yoshimura, Ph.D.

Research Overview

Our laboratory focuses on elucidating how T cells, particularly through the nuclear receptor NR4a, are involved in aging, cancer, and neurological diseases, with the ultimate goal of developing novel therapeutic strategies.

In a normal immune response, naïve T cells recognize pathogens or tumor cells, proliferate, and differentiate into effector T cells that eliminate the foreign antigens. Most effector T cells are short-lived, but a fraction differentiates into memory T cells, contributing to secondary immune protection and maintenance of homeostasis. It is well known that memory T cells are hierarchically classified into subsets such as central memory (T_{CM}) and effector memory (T_{EM}) cells. Recently, a new subset called stem cell memory T cells (T_{SCM})—long-lived, self-renewing cells that can replenish the memory pool—has been proposed and is gaining recognition. Increasing the number of TSCM is considered critical for inducing effective vaccine responses and potent antitumor immunity. Moreover, the importance of TCF1 (gene name *TCF7*)-positive stem-like memory T cells in tumor and infection sites has also been highlighted.

In contrast, under pathological conditions such as chronic infection and cancer, persistent T cell receptor (TCR) stimulation leads to a phenomenon known as T cell exhaustion (T_{EX}), mainly in $CD8^+$ T cells. Exhausted T cells highly express inhibitory molecules such as PD-1, CTLA-4, Tim-3, Lag-3, Nr4a, Tox, and SOCS, resulting in a hyporesponsive state that contributes to chronic infection and reduced antitumor immunity. Recent evidence also suggests their involvement in neurological disorders such as Alzheimer's disease. Furthermore, a study by Professor Nakanishi's group at the University of Tokyo demonstrated that blocking PD-1 enhances the clearance of senescent cells, thereby promoting organismal rejuvenation (***Nature*** 2022; 611(7935):358–364). These findings indicate that $CD8^+$ cytotoxic T cells play a crucial role in eliminating senescent cells, similar to their role in killing tumor cells. Although exhausted and senescent T cells differ in origin, they share several features, including high PD-1 expression. While many studies have described the characteristics of senescent and exhausted T cells, their fundamental causes and environmental triggers remain largely unclear.

We have identified the transcription factor Nr4a as a key regulator of the differentiation and function of senescent and exhausted T cells.

The NR4a family consists of three nuclear orphan receptor-type transcription factors: NR4a1 (also known as NUR77), NR4a2 (NURR1), and NR4a3 (NOR1). We previously reported that NR4a genes are essential for the development and maintenance of regulatory T cells (Tregs) (***iScience*** 2021; 24(3):102166; ***J Immunol 2022***; 208(9):2122–2130). NR4a binds to the promoters of Foxp3 in $CD4^+$ T cells and PD-1 or Tim-3 in $CD8^+$ T cells, upregulating their expression. Conversely, NR4a competes with AP-1 and NF-κB, thereby suppressing effector cytokines such as IFN-γ and TNF-α. Another group has reported that NR4a is also involved in T cell anergy, a key mechanism of immune tolerance.

Chromatin regions specifically open in exhausted T cells expressing PD-1 or Tim-3 contain consensus binding motifs for NFAT and

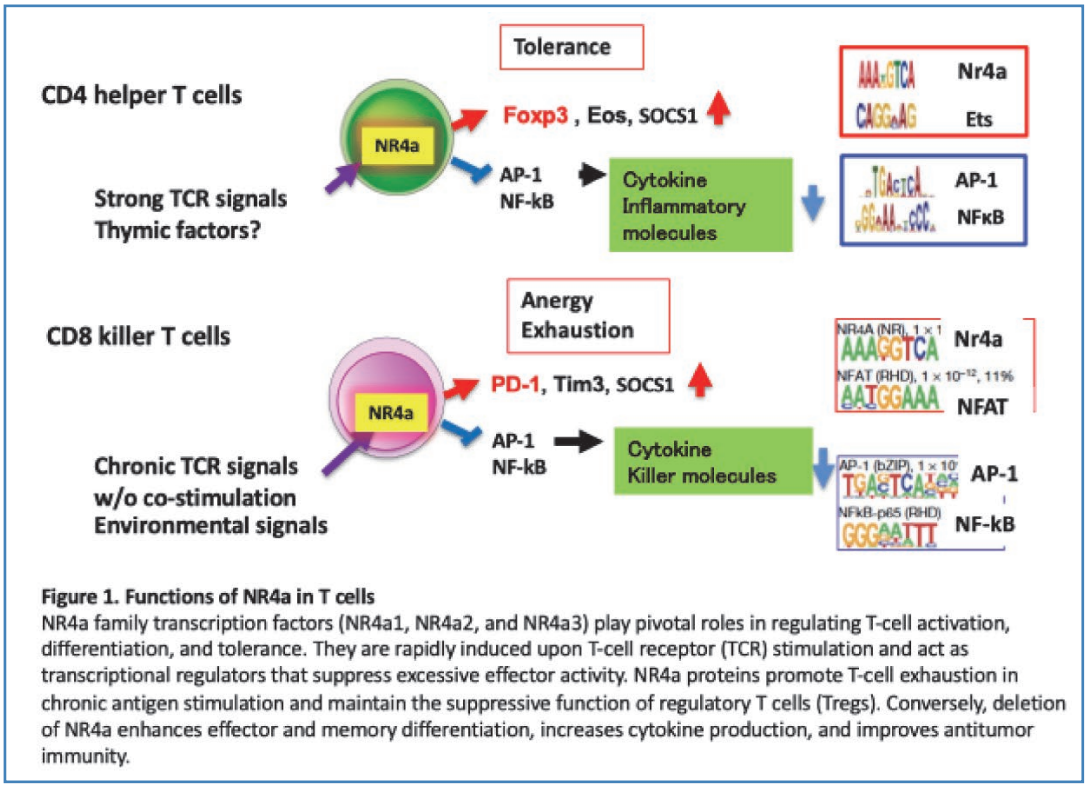

Figure 1. Functions of NR4a in T cells
NR4a family transcription factors (NR4a1, NR4a2, and NR4a3) play pivotal roles in regulating T-cell activation, differentiation, and tolerance. They are rapidly induced upon T-cell receptor (TCR) stimulation and act as transcriptional regulators that suppress excessive effector activity. NR4a proteins promote T-cell exhaustion in chronic antigen stimulation and maintain the suppressive function of regulatory T cells (Tregs). Conversely, deletion of NR4a enhances effector and memory differentiation, increases cytokine production, and improves antitumor immunity.

NR4a family members. Through a collaboration with Dr. Anjana Rao at the La Jolla Institute for Immunology (USA), we demonstrated that the NR4a family acts as a critical transcriptional regulator of T cell exhaustion (***Nature*** 2019; 567:530–534). Functions of NR4a are summarized in **Figure 1**.

NR4a converts T cell fate in the tumor in mice

These findings suggest that inhibition of NR4a could enhance antitumor immunity. We therefore generated $CD8^+$ T cell specific NR4a1/2 conditional knockout mice (CD8-Cre) and analyzed tumor-bearing models. Deletion of NR4a1/2 in $CD8^+$ T cells reduced the population of exhausted T cells in tumor-infiltrating lymphocytes (TILs) and elicited potent antitumor effects.

Interestingly, single-cell RNA sequencing (scRNA-seq) revealed that loss of NR4a1/2 not only reduced exhausted T cell clusters but also increased $TCF1^+$ stem-like precursor populations, suggesting that NR4a deletion may revert exhausted T cells to a more youthful, memory-like state.

To investigate this, we established a serial adoptive transfer model. $CD8^+$ T cells isolated from OT-I transgenic ERT2-Cre NR4a1/2-flox mice were transferred into Rag2-deficient mice bearing B16 melanoma cells expressing OVA. After 10 days, $PD\text{-}1^+Tim\text{-}3^+$ exhausted T cells were isolated from TILs and transferred again with B16-OVA cells into secondary Rag2-deficient hosts. Upon tamoxifen (TAM) treatment to delete NR4a1/2, tumor growth was significantly reduced. Without TAM, the transferred exhausted T cells failed to proliferate and disappeared, whereas TAM-treated mice showed T cell expansion with re-emergence of $PD\text{-}1^+Tim\text{-}3^-$ subsets. scRNA-seq comparison of pre-transfer and post-TAM T cells identified two new clusters with high Tcf7 expression, suggesting that loss of NR4a can reprogram exhausted T cells into stem-like progenitors (T_{PEX}) (***Cell Rep.*** 2024; 43(3):113898)(**Figure 2**).

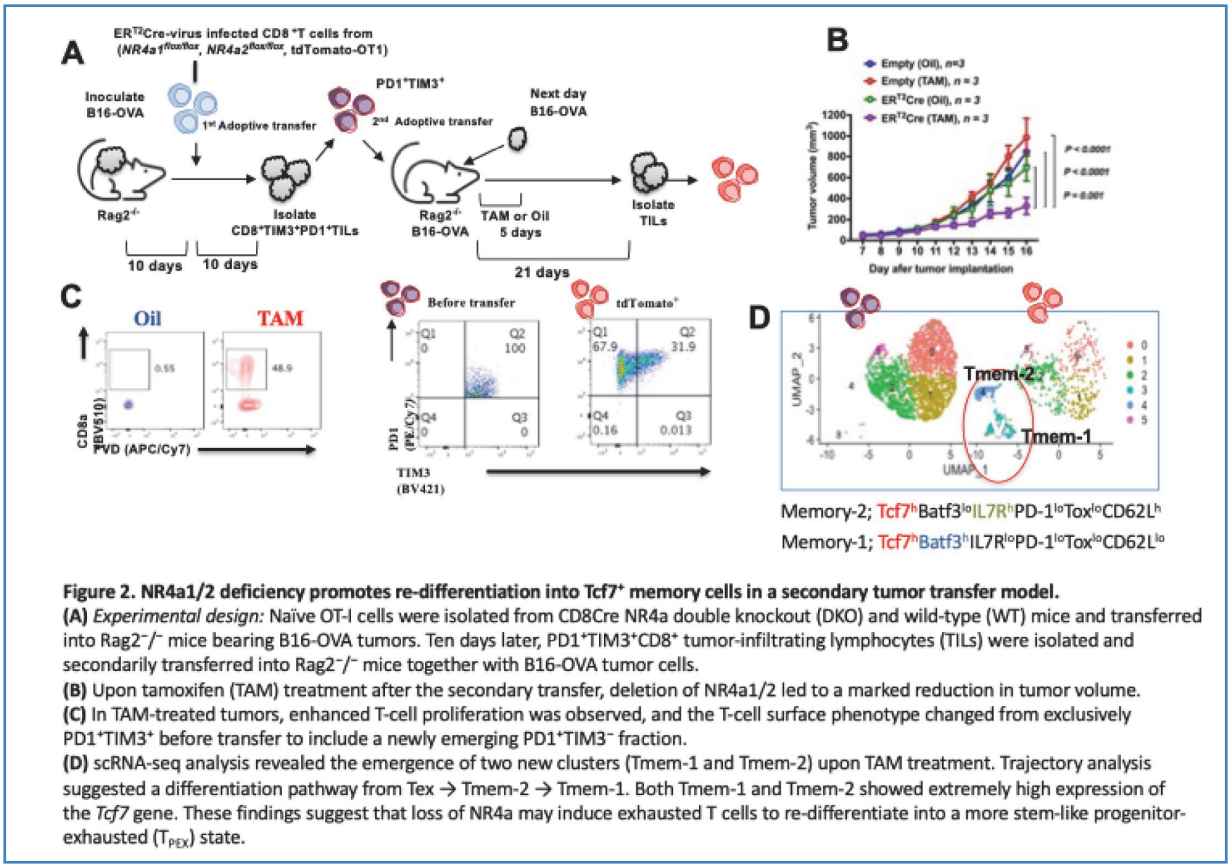

Figure 2. NR4a1/2 deficiency promotes re-differentiation into Tcf7⁺ memory cells in a secondary tumor transfer model.
(A) *Experimental design:* Naïve OT-I cells were isolated from CD8Cre NR4a double knockout (DKO) and wild-type (WT) mice and transferred into Rag2^{-}/$^{-}$ mice bearing B16-OVA tumors. Ten days later, PD1⁺TIM3⁺CD8⁺ tumor-infiltrating lymphocytes (TILs) were isolated and secondarily transferred into Rag2^{-}/$^{-}$ mice together with B16-OVA tumor cells.
(B) Upon tamoxifen (TAM) treatment after the secondary transfer, deletion of NR4a1/2 led to a marked reduction in tumor volume.
(C) In TAM-treated tumors, enhanced T-cell proliferation was observed, and the T-cell surface phenotype changed from exclusively PD1⁺TIM3⁺ before transfer to include a newly emerging PD1⁺TIM3⁻ fraction.
(D) scRNA-seq analysis revealed the emergence of two new clusters (Tmem-1 and Tmem-2) upon TAM treatment. Trajectory analysis suggested a differentiation pathway from Tex → Tmem-2 → Tmem-1. Both Tmem-1 and Tmem-2 showed extremely high expression of the *Tcf7* gene. These findings suggest that loss of NR4a may induce exhausted T cells to re-differentiate into a more stem-like progenitor-exhausted (T_{PEX}) state.

Collaborators:

Minako Ito, Makoto Ando, Kensuke Nakagawara and Tanakorn Srirat

Generation of NR4a-Deficient Human CAR-T Cells and Their Antitumor Effects

We further demonstrated that deletion of all three NR4a genes in human CAR-T cells confers robust antitumor activity against solid tumors.

To induce exhaustion in vitro, we established a continuous antigen exposure (CEA) system, in which HER2 CAR-T cells were repeatedly cocultured with HER2^{+} tumor cells. Wild-type (WT) CAR-T cells stopped proliferating after 3–4 cocultures, showing complete exhaustion characterized by reduced cytokine production, loss of naïve markers, and upregulation of exhaustion markers.

In contrast, NR4a triple knockout (TKO) CAR-T cells continued to proliferate for over 20 days, maintained cytokine production, and showed minimal expression of exhaustion markers. Similar results were obtained with T cells derived from elderly donors. Comparative analysis of single, double, and triple knockouts revealed that triple NR4a deficiency provided the strongest resistance to exhaustion and the most potent antitumor effects.

In NSG mouse xenograft models, NR4a TKO CAR-T cells exhibited powerful antitumor activity and significantly improved survival. These findings, together with accumulating reports that NR4a inhibitors reduce solid tumor growth, identify NR4a as a promising therapeutic target for cancer immunotherapy (***J Immunother Cancer.*** 2024; 12(8):e008665)(**Figure 3**).

Collaborators:

Kensuke Nakagawara, Minako Ito, Makoto Ando and Tanakorn Srirat

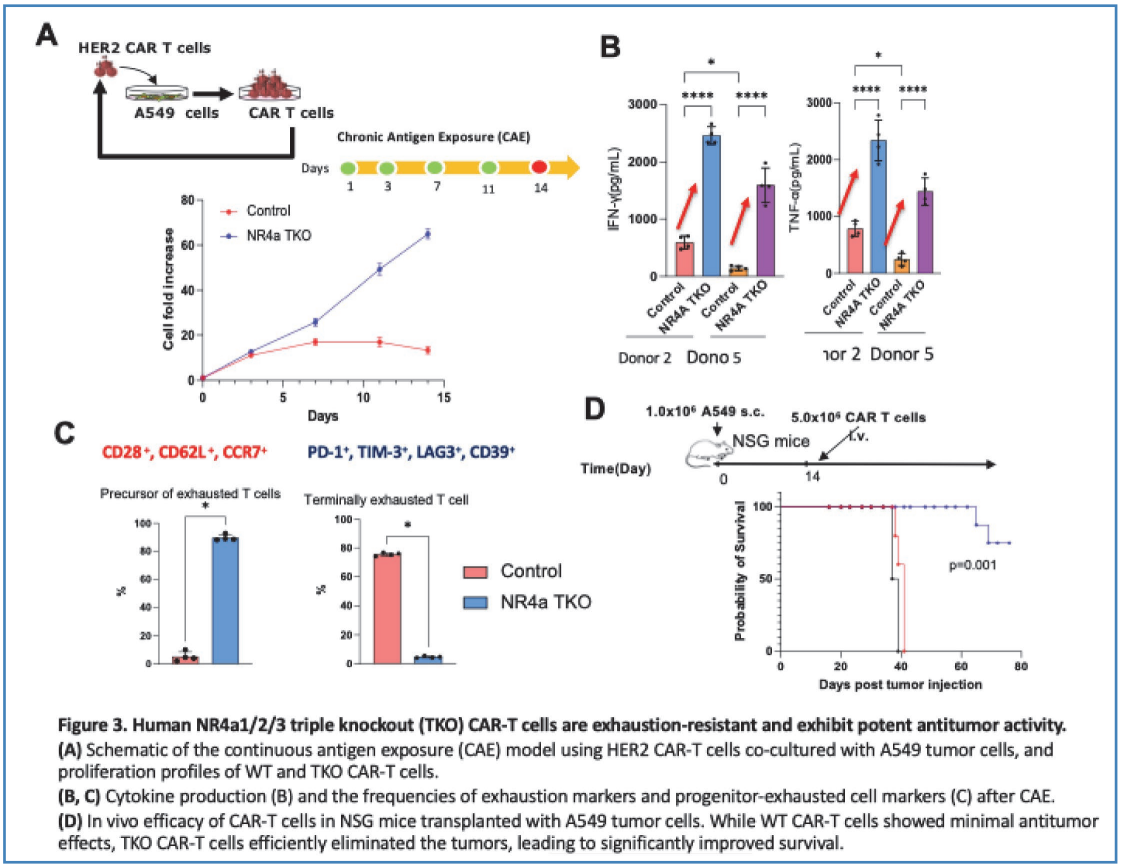

Figure 3. Human NR4a1/2/3 triple knockout (TKO) CAR-T cells are exhaustion-resistant and exhibit potent antitumor activity.
(A) Schematic of the continuous antigen exposure (CAE) model using HER2 CAR-T cells co-cultured with A549 tumor cells, and proliferation profiles of WT and TKO CAR-T cells.
(B, C) Cytokine production (B) and the frequencies of exhaustion markers and progenitor-exhausted cell markers (C) after CAE.
(D) In vivo efficacy of CAR-T cells in NSG mice transplanted with A549 tumor cells. While WT CAR-T cells showed minimal antitumor effects, TKO CAR-T cells efficiently eliminated the tumors, leading to significantly improved survival.

SPRED1 Mutations and Neuro-degenerative Disease

SPRED1 is a negative regulator of the Ras–ERK signaling pathway that localizes to membrane lipid rafts. It contains three domains: EVH1, KBD (c-Kit–binding domain), and SPR. The SPR domain undergoes palmitoylation, promoting its localization to lipid rafts, while the EVH1 domain binds to RasGAP domains (GRD) to inhibit Ras activation.

Loss-of-function mutations in human SPRED1 cause Legius syndrome, an autosomal dominant disorder. In this study, we identified eight pathogenic mutations within the SPR domain of SPRED1 cDNA from Legius syndrome patients that impair palmitoylation and disrupt membrane localization. Six variants, including the P415A mutation, formed cytoplasmic aggregates.

To assess the in vivo effects of this mutation, we generated Spred1-P415A knock-in (KI) mice. Immunostaining revealed that Spred1 is expressed in Purkinje cells of the cerebellum. Heterozygous P415A mice developed age-dependent cerebellar ataxia, while homozygous mutants exhibited Purkinje cell loss. Aggregated Spred1-P415A protein puncta and accumulation of p62, a marker of defective protein degradation, were observed in Purkinje cells.

These findings suggest that SPRED1 is a novel candidate gene for autosomal dominant cerebellar ataxia (***J Biol Chem.*** 2024; 300(12):107969.)(**Figure 4**).

Collaborators:

Yasuko Hirata, Hilde Brems, Seppe Van der Auweraer, Ludwine Messiaen, Eric Legius

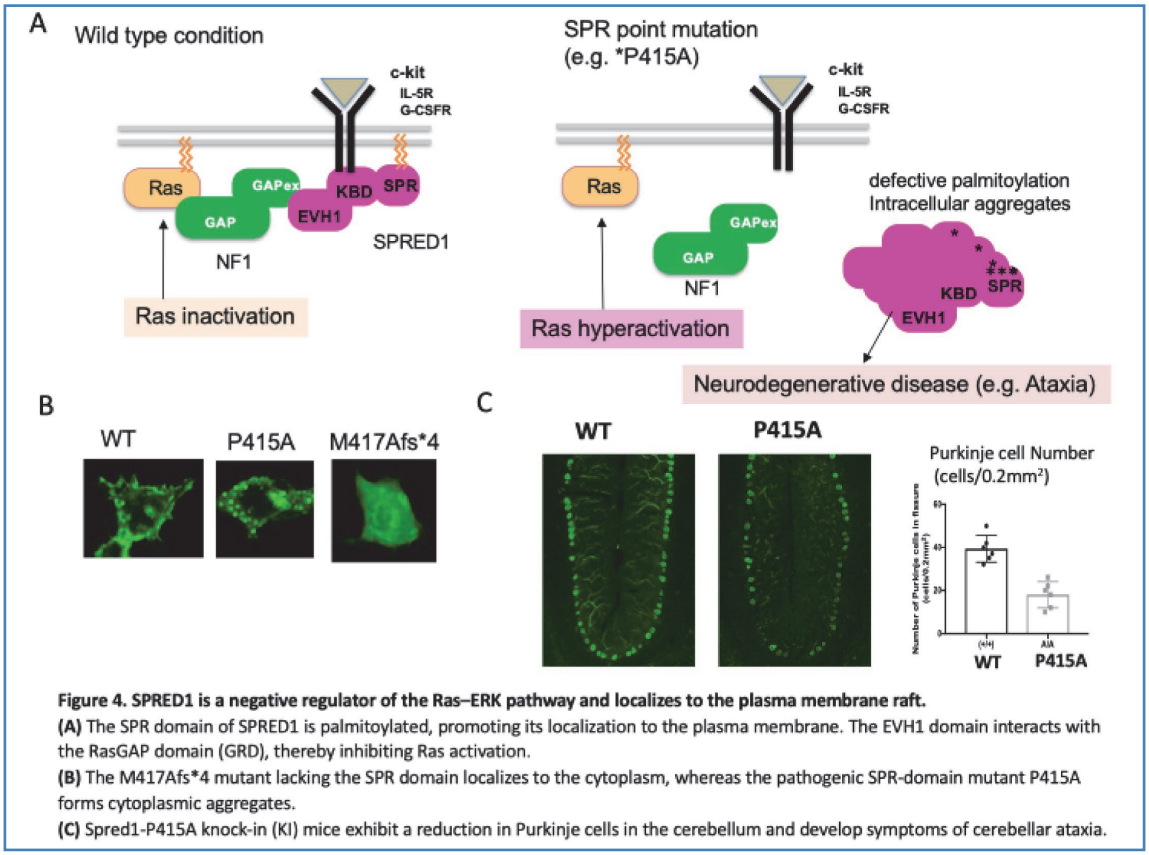

Figure 4. SPRED1 is a negative regulator of the Ras–ERK pathway and localizes to the plasma membrane raft.
(A) The SPR domain of SPRED1 is palmitoylated, promoting its localization to the plasma membrane. The EVH1 domain interacts with the RasGAP domain (GRD), thereby inhibiting Ras activation.
(B) The M417Afs*4 mutant lacking the SPR domain localizes to the cytoplasm, whereas the pathogenic SPR-domain mutant P415A forms cytoplasmic aggregates.
(C) Spred1-P415A knock-in (KI) mice exhibit a reduction in Purkinje cells in the cerebellum and develop symptoms of cerebellar ataxia.

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