Doctoral Dissertation Defense Announcement

“GATA2-TGF-β1-TAL1 axis is essential for human NK cell development”

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Microbiology and Immunology
School of Graduate Studies
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Committee in Charge:
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Joseph T. Barbieri, PhD
Scott Terhune, PhD
Sridhar Rao, MD, PhD
Wane Yokoyama, MD (External, WashU)

Date: Wednesday, Sep 4, 2024
Time: 9:00 AM (CST)
Defense Location: VBRI seminar room
Zoom: contact danwang@mcw.edu for zoom link.
Graduate Studies:
IDP program 1st year curriculum
Cellular & Molecular Immunology
Immunology Journal Club
Introduction to Biostatistics
Tumor Immunology
Immunology Seminar Course
Career development (Summer class)
Reading and Research
Ethics and Integrity in Science
Research Ethics Discussion Series
Doctoral Dissertation
Natural killer (NK) cells are the major innate cytotoxic lymphocytes that mediate rapid and robust effector responses against tumors and pathogens without prior sensitization. However, the transcriptional mechanisms involved in human NK cell development and functions are yet to be fully defined. The transcription factor (TF) GATA2 is essential for regulating the survival, proliferation, and differentiation of hematopoietic stem cells (HSCs) and NK cell development. GATA2 forms a chromatin-bound heptad complex with other TFs (TAL1, FLI1, RUNX1, LYL1, LMO2, and ERG), to regulate hundreds of target genes in HSCs, which are lineage and stage-specific. Heterozygous GATA2 pathogenic variants cause monocytopenia with atypical mycobacterial infection; dendritic cells, monocytes, B and NK lymphocyte deficiency (DCML); familial myelodysplastic syndrome/acute myeloid leukemia (MDS/AML); and Emberger syndrome (consists of MDS, lymphedema, and warts from human papillomavirus infection). GATA2 mutation results in the reduction of CD56^{Bright} NK cells with/without reduced CD56^{Dim} NK cells. Variants, including T354M in the second DNA-binding zinc finger domain, impair human NK cell development and function.

TAL1, a class II basic helix-loop-helix TF, plays an essential role in early hematopoiesis along with GATA2. Germline deletion of Tal1 in mice leads to failure to develop HSCs. TAL1 forms an obligate heterodimer with E proteins, including E2A and HEB. TAL1 is silenced before the CD4-CD8^- T cell progenitors commit to the double-positive stage, where HEB or E2A support T cell commitment. ID2, an essential TF for NK cells, blocks HEB DNA binding, blocks transcription of T cell-associated genes, and promotes NK cell commitment. Id2 disrupts assembly of an E2a-TAL1 transcriptional complex and modulates chromatin accessibility of select promoter regions in mice, thus implicating an essential role for TAL1 in NK cell development. Irrespective of these findings, the role of TAL1 or GATA2-TAL1 complex in NK cell development and function is unknown.

TGF-β1 regulates HSC quiescence and self-renewal and homeostasis of the immune system, especially within the BM niche. Importantly, human primary NK cells produce significant amounts of TGF-β1 compared to other lymphocytes. TGF-β1 stimulates the proliferation of myeloid-biased HSCs but inhibits the growth of lymphoid-biased HSCs. TGF-β1 sustains the stemness of CD34^+ HSCs by pausing the commitment into NKPs. TGF-β1 also functions as a checkpoint to maintain NK cell immaturity at the CD56^{Bright} stage. However, it is unknown how TGF-β1 transcriptionally regulates human NK cell development and whether there are any links between GATA2 and TGF-β1.

In this study, we identified a GATA2-TAL1-TGF-β1 axis that is essential for human NK cell development and maturation. We found that primary human NK cells express high levels of TAL1, and TAL1 and its target genes were significantly
upregulated in NK cells from patients with GATA2 pathogenic variants and GATA2 variant-expressing cells. GATA2 repressed TAL1 transcription, whereas GATA2$^{T354M}$ failed to repress TAL1. In contrast, GATA2$^{T354M}$ substantially reduced the expression of TGFB1 and known TGF-β1 target genes in human NK cells. Mechanistically, we identified two GATA motifs in the proximal promoter region of the TGFB1 gene. In vitro, luciferase reporter assay demonstrated GATA2 regulation of the TGFB1 promoter. ATAC-seq and CUT&Tag assays using human primary NK cells revealed GATA2 occupied the TGFB1 promoter, and occupancy was associated with H3K4me3, an active promoter mark. Thus, GATA2-mediated regulation of TGFB1 at an early commitment stage permits an orderly and successful transition of early NK cell developmental stages. TGF-β1 stimulated TAL1 degradation, suggesting that a decrease in TGF-β1 with a concomitant increase in TAL1 formed the mechanistic basis for defective NK cell development in patients with the GATA2$^{T354M}$ variant. The interplay between GATA2, TGF-β1, and TAL1 provides an important missing link required for early human NK cell development.
Dandan Wang  
Curriculum Vitae  
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**Education**

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<tr>
<th>Medical College of Wisconsin</th>
<th>Ph. D. in Immunology</th>
<th>08/2018-current</th>
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<td>Wisconsin, WI, US</td>
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<tr>
<th>Shanxi Medical University</th>
<th>MBBS. &amp; MMed. in Internal Medicine</th>
<th>09/2009-07/2016</th>
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<td>Shanxi, Taiyuan, China</td>
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**Research Experience**

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<tr>
<th>Graduate Student Research Assistant</th>
<th>2018-current</th>
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<td>Subramaniam Malarkannan lab, Medical College of Wisconsin</td>
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<tr>
<th>Visiting Research Trainee</th>
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<td>Margret Wong-Riley lab, Medical College of Wisconsin</td>
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<th>Master Student in Clinical Research</th>
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<th>Medical Student Research volunteer</th>
<th>2011-2016</th>
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<td>Jin-shun Qi lab, Shanxi Medical University</td>
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**Awards and Honors**

- 2023: American Society of Hematology (ASH) Abstract Achievement Award
- 2023: Versiti-BRI Education Committee Award
- 2023: Versiti-BRI Immunology Program Trainee Award
- 2023: MCW Grad Student Association Symposium Oral Presentation Award
- 2023: DOM Health Foundation Travel Award
- 2023: MCW Graduate Student Travel Award
- 2023: Versiti-BRI Immunology Program Trainee Award
- 2022: MCW Center for Immunology Fall Travel Award, Medical College of Wisconsin
- 2022: American Society of Hematology (ASH) Abstract Achievement Award
- 2022: BizTimes Notable Women in Healthcare
- 2022: American Society of Hematology (ASH) Abstract Achievement Award
- 2015: Shanxi Province Academic Fellowship for Postgraduates, China
- 2010: National Endeavor Fellowship (Top 5%), China
- 2009-2016: Shanxi Medical University Scholarships, China

**Grant**

- 2022-2024: Predoctoral fellowship from American Society of Hematology (ASH) Graduate Hematology Award ($80,000)
- 2022: MCW Center for Immunology, Growth and Research in Immunology Training (GRIT) Award ($15,000)

**EDITORIAL BOARDS/JOURNAL REVIEWS:**

Peer Review for Journals: *EMBO, Frontiers in Immunology, Journal of Scientific Report, Frontiers in Tumor Immunology*
Publications:

Research articles


Research articles in preparation

1. Human primary NK cell mRNA delivering by lipid nanoparticle for future cell therapy potential. **Dandan Wang***, Katherine Badior*, Subramaniam Malarkannan*, Christian Kastrup* [In preparation].

2. Context-dependent transcriptomic alterations dictate the outcome of hematopoiesis in GATA2-ZF1 or ZF2 mutated patients. **Dandan Wang**, Kasiani Myers, and Subramaniam Malarkannan [In preparation].


4. SBRT facilitates immune promoting TME in PDAC patients. **Dandan Wang**, Susan Tsai, Matthew Riese, William Hall, and Subramaniam Malarkannan [In preparation].

Review articles


Methodology articles


Research articles prior to Ph.D. training


Presentations in Regional, National, and International forums

Dec. 2023: The 65th American Society of Hematology Annual Meeting & Exposition, San Diego, California

**Oral presentation:** A novel GATA2-TAL1 axis is essential for human NK cell development and function.

Apr 2023: The 6th Annual GSA Symposium, Milwaukee, Wisconsin

**Oral presentation:** A novel GATA2-TGF-b1 axis is essential for human NK cell development.

Mar 2024: 2024 MCW Cancer Center Trainee Symposium, Milwaukee, Wisconsin

**Poster presentation:** A novel GATA2-TGF-b1-TAL1 axis is essential for human NK cell development and function.
Apr. 2024: Versiti-BRI scientific retreat, Milwaukee, Wisconsin
Poster presentation: A novel GATA2-TGF-b1-TAL1 axis is essential for human NK cell development and function.

Sep 2023: Versiti-BRI SAB poster event, Milwaukee, Wisconsin
Poster presentation: A novel GATA2-TGF-b1-TAL1 axis is essential for human NK cell development and function.

May 2023: The 106th Annual Meeting of American Association of Immunologists
Poster Presentation: GATA2-TGF-b1 axis regulates human NK cell development

Dec. 2022: The 64th American Society of Hematology Annual Meeting & Exposition, New Orleans, Louisiana, US.
Poster presentation: A novel GATA2-TGF-b1 axis is essential for human NK cell development.

Poster presentation: Neck Circumference - a new predicting measurement of BMC.

Poster presentation: Antidepressant Desipramine Prevents Ab-Induced Cognitive Deficit, Mental Depression and p-CREB Reduction in Mice.