WHIM Syndrome: A Misguided Immune System!

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Resource Information

About This Resource

These slides are one component of a continuing education program available online at MedEd On The Go titled WHIM Syndrome (A Chronic Neutropenic Disorder): Uncouple the Complex for HCPs and Patients

Program Learning Objectives:

- Gain an understanding of WHIM syndrome as a rare PID/ chronic neutropenic disorder with diverse clinical presentations
- Implement strategic measures to improve the early identification of WHIM syndrome patients for prompt assessment and diagnosis to avoid potential complications and long-term sequelae
- Understand the CXCR4 pathway dysregulation and how it relates to the underlying causes of WHIM syndrome
- Garner an understanding of the limitations of current approaches for WHIM syndrome and potential new approaches for patients

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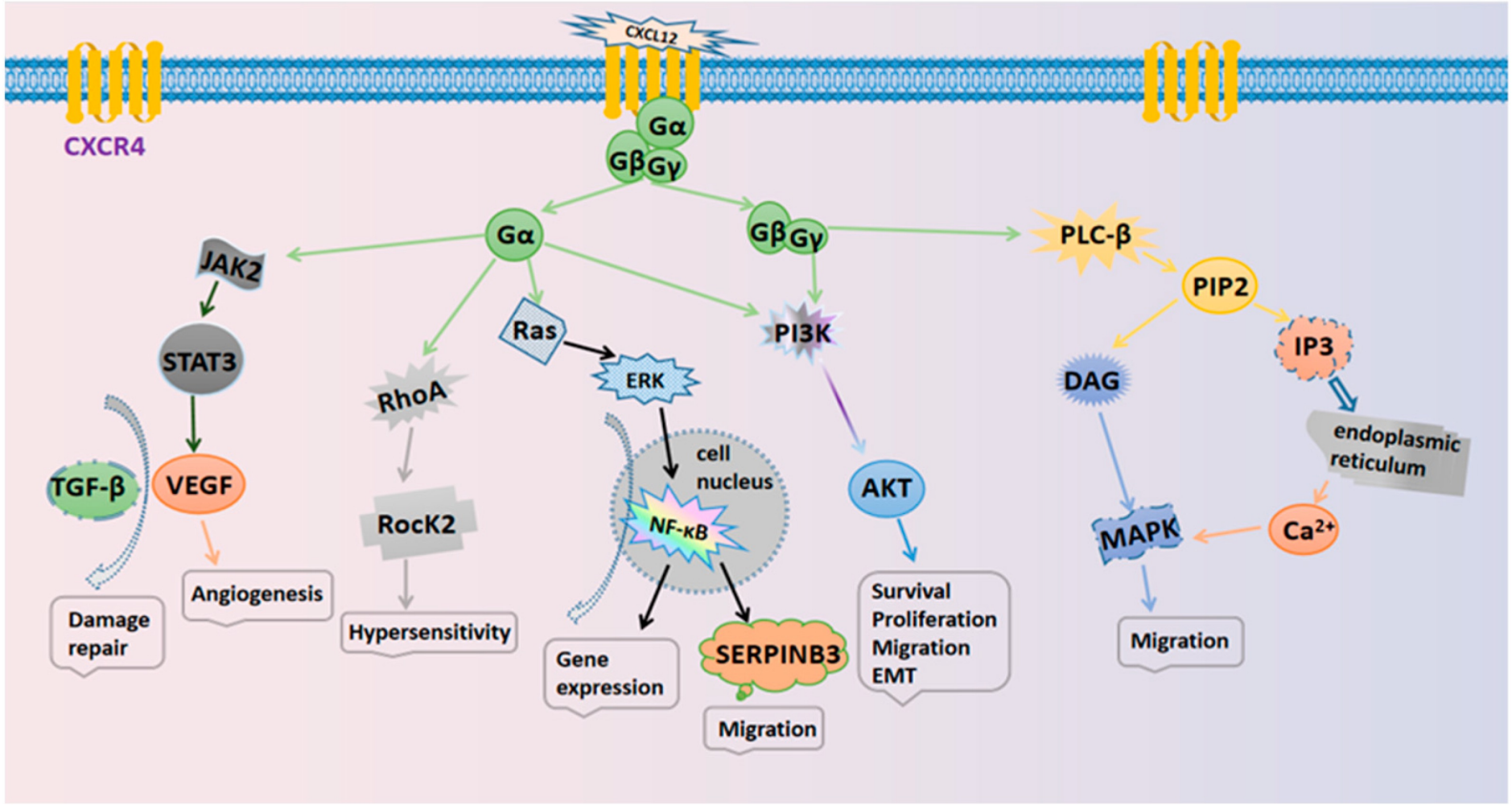
- CXCR4 receptor, upon binding its ligands (primarily CXCL12), triggers multiple signaling pathways that orchestrate cell migration, hematopoiesis and cell homing, and retention in the bone marrow



Front Immunol. 2015; 6: 429.

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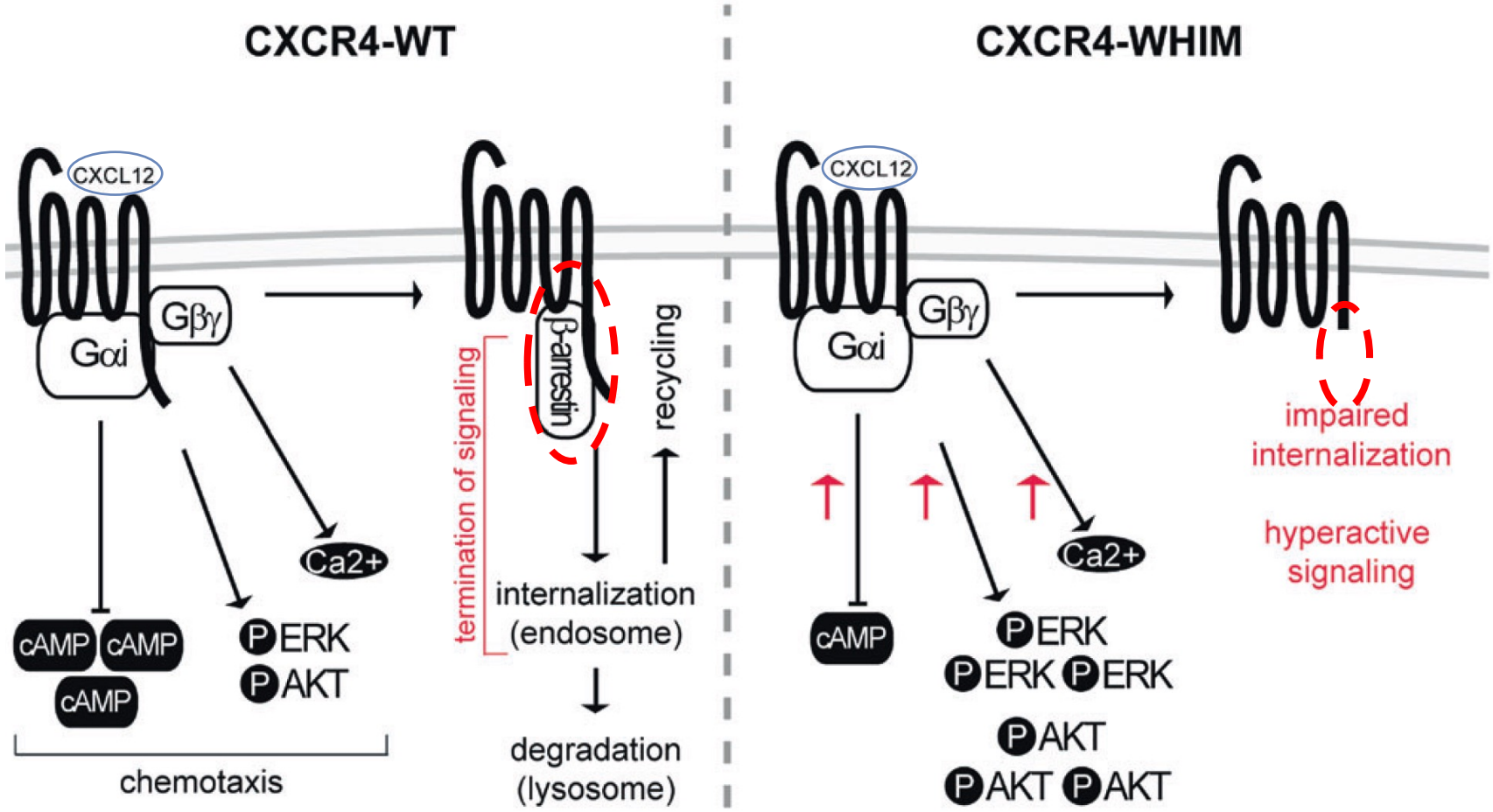

Truncation of CXCR4 with loss of cytoplasmic tail prevents β-arrestin binding, internalization, and degradation.

This results in hyperactive signaling.

Immune cells have abnormal trafficking and function.

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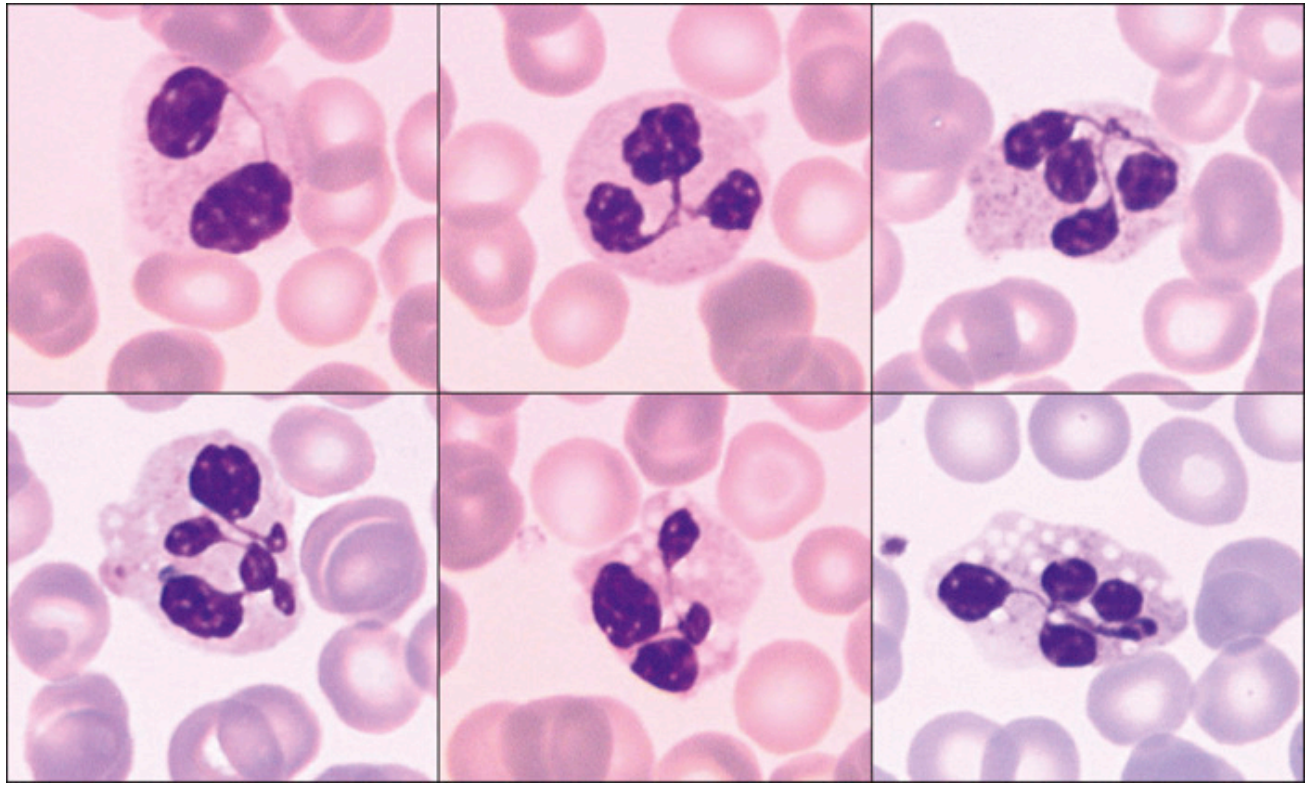
CXCR4 gain of function affects:

- Neutrophils
- B cells
- T cells
- Dendritic cells

Resulting in broad spectrum of immunodeficiency and characteristic neutrophil morphology of myelokathexis



Geier CB, et al. *J Clin Immunol*. 2022; 42(8): 1748–1765;
Bledsoe JR, et al. *Blood*. 2022; 5487-5489.

Strategic Measures to Improve the Identification of Under-Recognized Diverse Presentations of WHIM Syndrome for Prompt Assessment and Diagnosis

- Don’t wait for all 4 features of WHIM to consider the diagnosis
- Neutropenia and infections are the most common presenting features, but not universal
- Younger is better
- Test every newborn with a family history of WHIM, regardless of lab results or clinical condition

Diagnostic Approach

- Immunology approach:
  - Lymphocyte subsets
  - Immunoglobulin levels
  - IgG responses to vaccines
- Hematology approach:
  - Repeated CBC/diff for ANC and ALC
  - Peripheral blood smear, bone marrow examination – NOTE: Myelokathexis in PB or BM is diagnostic but easily missed and not always present
- **GENETIC** approach

ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

Genetic Approach to Diagnosis of WHIM

- *CXCR4* sequencing: Appropriate for family history of WHIM
- NGS panel
  - *CXCR4* is included in most NGS panels for neutropenia, IEI or PID
  - IEI or PID panels recommended, as broader in scope
  - Allows detection of other inherited disorders with overlapping phenotypes
  - Invitae IEI panel is available without charge in a sponsored program for suspicion of WHIM: https://www.invitae.com/us/sponsored-testing/path4ward
- Consider whole exome or whole genome sequencing if *CXCR4* is normal, i.e., WHIM-like syndrome

IEI, inborn errors of immunity; NGS, next generation sequencing; PID, primary immune deficiency.

Balabanian K, et al. *J Clin Invest*. 2008; 118:1074; Geier CB, et al. *J Clin Immunol*. 2022; 42(8):1748-1765; Furutani E, et al. *Am J Hematol*. 2019; 94(3):384-393.

Consider WHIM When Newborn Screen Shows Decreased TRECs

REVIEW ARTICLE

Can we identify WHIM in infancy? Opportunities with the public newborn screening process

Melis Yilmaz, David Evan Potts, Christoph Geier, Jolan E. Walter

First published: 09 October 2022 | https://doi.org/10.1002/ajmg.c.32002

- TRECs are detected by PCR using DNA from dried blood spots
- TREC levels are used as a biomarker for thymic output, as TRECs emerge as a by-product of TCR V(D)J gene rearrangement during T-cell development
- Finding of decreased TRECs is sensitive for SCID, but not specific
- In retrospective study of 6 infants with WHIM, 3 had significantly decreased TRECs on newborn screens
- WHIM should be on the differential diagnosis of decreased TRECs and normal screening for SCID. Do not dismiss as false positive!

PCR, polymerase chain reaction; SCID, severe combined immunodeficiency; TCR, T cell receptor; TRECs, T-cell receptor excision circles.

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