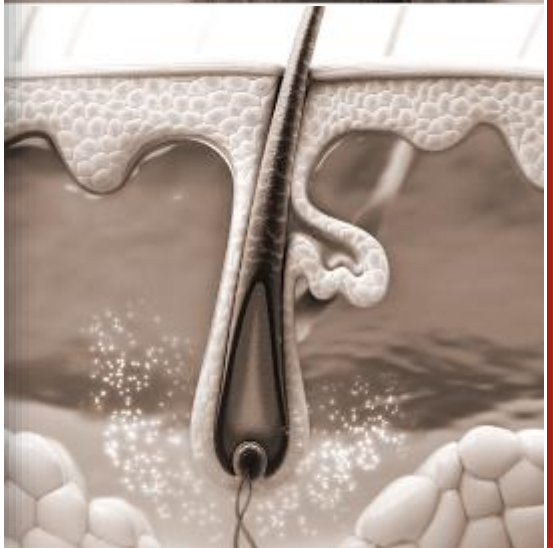
Alopecia Areata Mechanism of Disease

Chapter 1

Introduction & Unmet Needs in Alopecia Areata



Defining AA

- **Alopecia areata**, or AA, is an autoimmune hair loss disorder[1]
- AA causes well-defined coin-shaped patches of nonscarring hair loss[1]

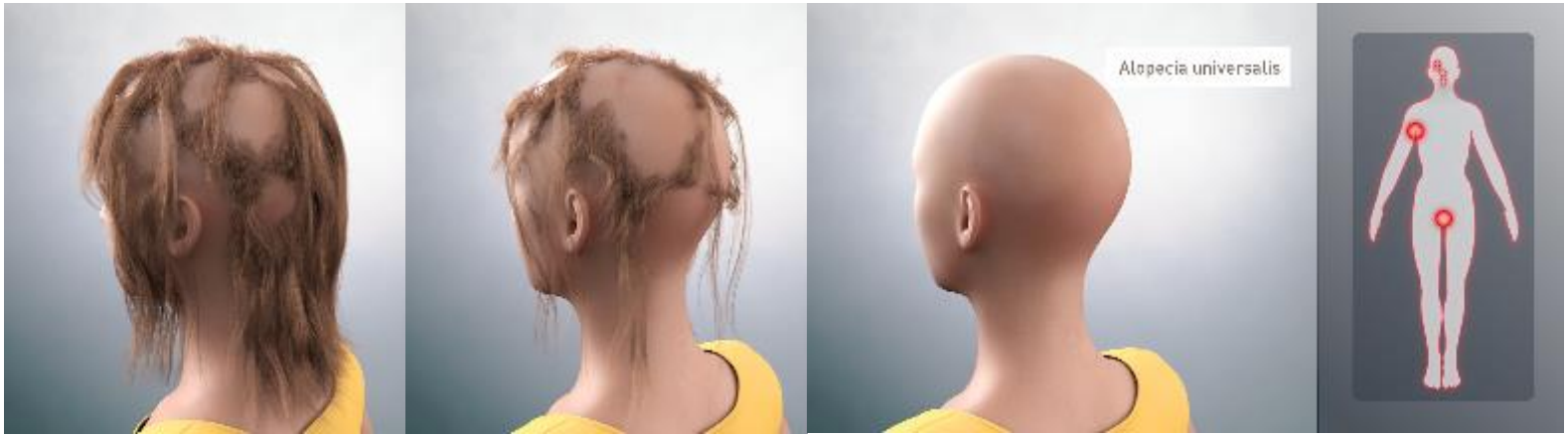
1. Pratt CH, et al. *Nat Rev Dis Primers.* 2017;3:17011.

Presentation and Prevalence

Hair loss in AA is varied and can include[1]:

- Single well-defined patches
- Multiple discrete or overlapping patches
- Loss of hair in all hair-bearing sites, known as alopecia universalis

AA affects nearly 2% of the population[2]



1. Pratt CH, et al. *Nat Rev Dis Primers.* 2017;3:17011; 2. Strazzula LC, et al. *J Am Acad Dermatol.* 2018a;78:1-12.

Comorbidities

Common comorbid disorders associated with AA include[1-3]:

Atopic dermatitis[3]

Thyroid disease[1]

Allergic rhinitis[1]

Vitiligo[3]

1. Chu SY, et al. *J Am Acad Dermatol*. 2011;65(5):949-956; 2. Lee NR, et al. *Ann Dermatol*. 2014;26(6):722-726; 3. Drucker AM, et al. *Allergy*. 2017;72(5):831-834.

Psychiatric Comorbidities

- Alopecia areata is also associated with psychiatric comorbidities such as **anxiety** and **depression**, affecting patients' quality of life[1]

1. Lee S, et al. *J Am Acad Dermatol*. 2019;80:466-477.

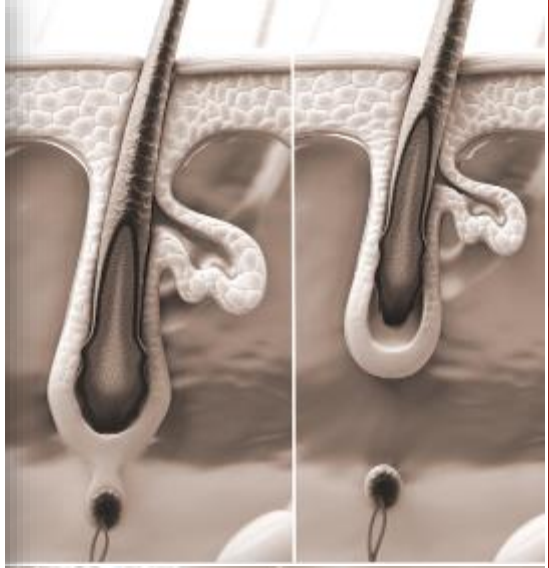
Complex Etiology

- AA has a complex etiology with an unpredictable disease course, making management difficult[1]

1. Pratt CH, et al. *Nat Rev Dis Primers.* 2017;3:17011.

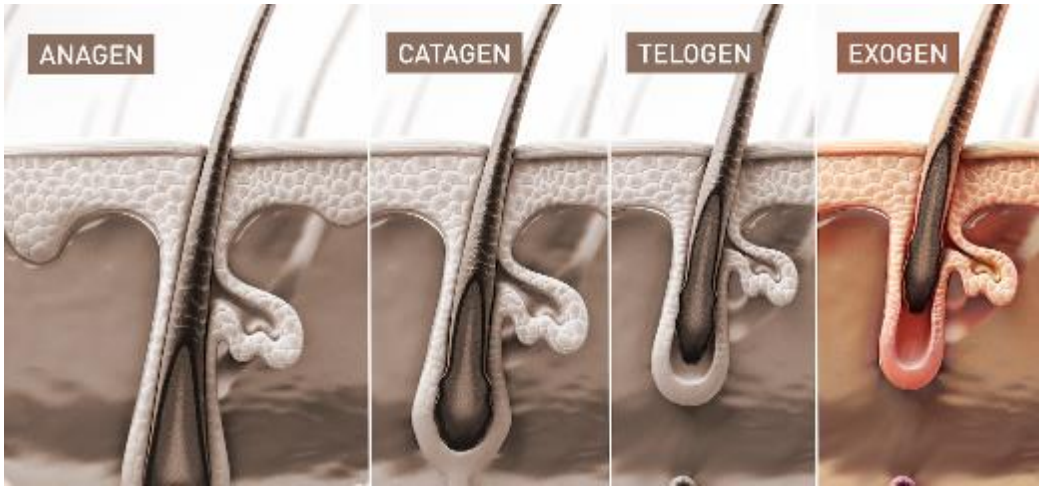
Chapter 2

Mechanism of Disease of Alopecia Areata



The Human Hair Cycle

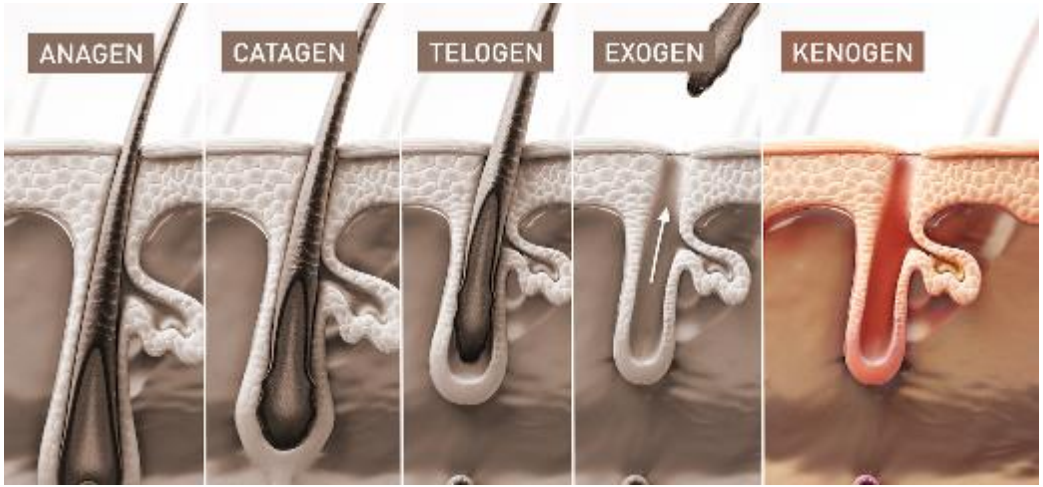
- **The human hair cycle has four distinct phases[1,2]:**
  - **Anagen** is the growth phase
  - **Catagen** is the transitional phase
  - **Telogen** is the resting phase, where hair is shed towards the end
  - **Exogen** is the phase where the follicle remains empty until the onset of the next anagen phase



1. Cotsarelis G, Botchkarev V. Fitzpatrick's Dermatology. 9th ed. McGraw-Hill Education; 2019:89-105; 2. Higgins CA, et al. *J Invest Dermatol*. 2009;129(9):2100-2108.

AA Disrupts the Hair Cycle

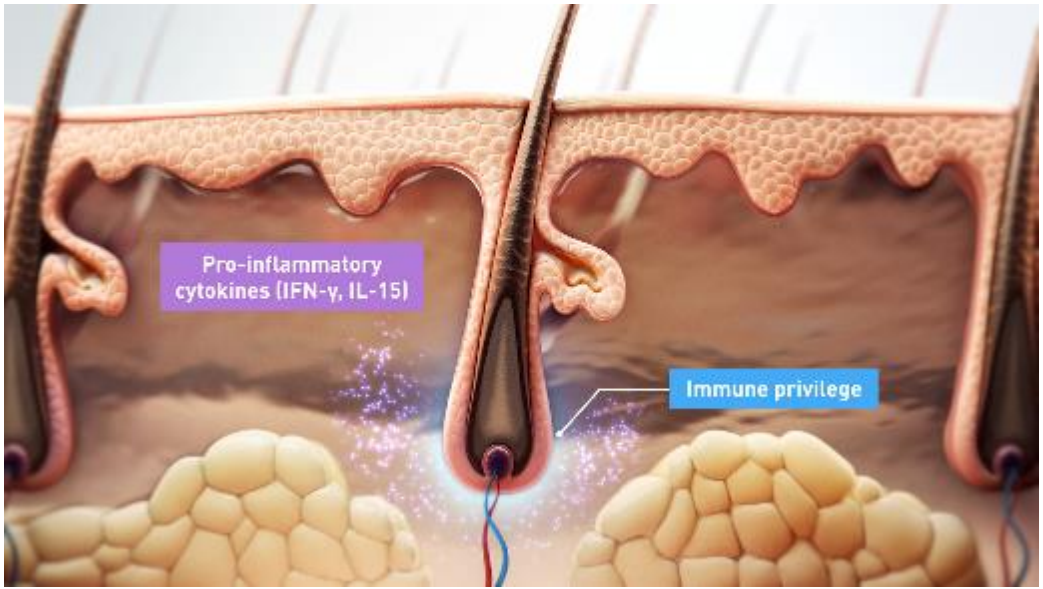
- In AA, the cyclical nature of hair growth is disrupted[1]
- Hair prematurely leaves the anagen phase and transitions through the catagen, telogen, and exogen phases[2]
- It then enters the **kenogen phase**, where the hair follicle remains empty and does not re-enter the growth phase[1,3]



1. Bhat YJ, et al. *Hair Ther Transplant.* 2014;4:2; 2. Pratt CH, et al. *Nat Rev Dis Primers.* 2017;3:17011; 3. Rebora A, Guarrera M. *Dermatology.* 2002;205(2):108-110.

Loss of Hair Follicle Immune Privilege

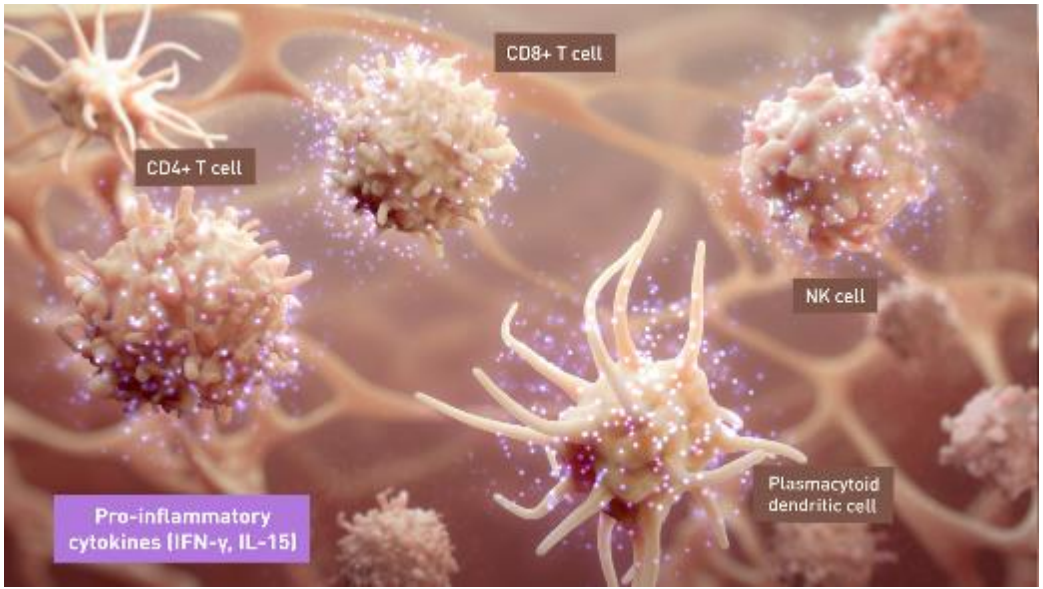
- The pathogenesis of AA and the interference of the hair growth cycle are believed to be phenomena resulting from loss of hair follicle immune privilege[1]



1. Ito T. *Clin Dev Immunol.* 2013;2013:348546.

Immune Privilege

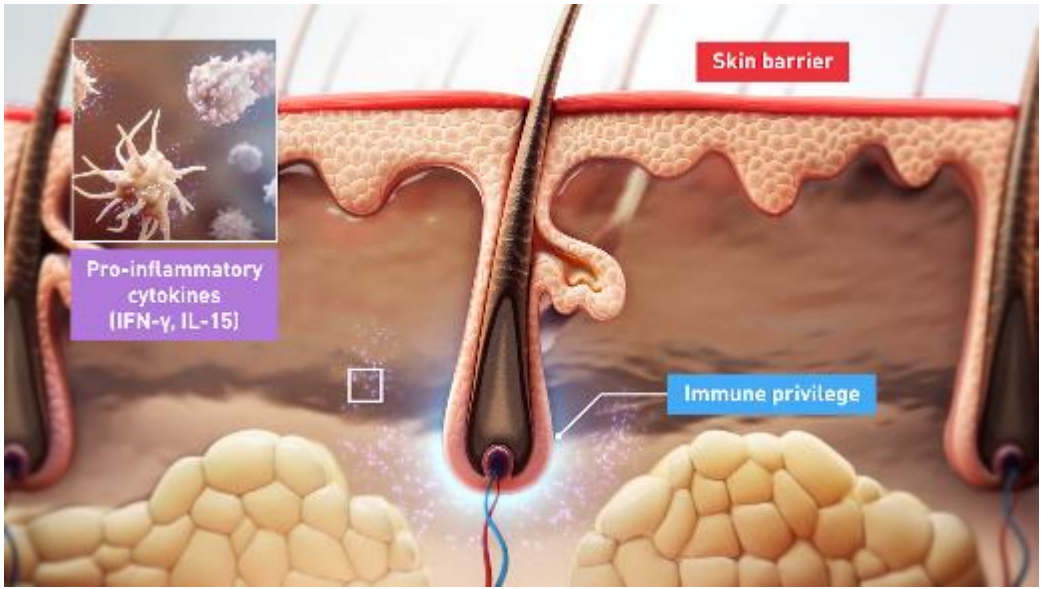
- Immune privilege is a complex mechanism that suppresses inflammation and promotes immune tolerance in the hair follicle[1,2]



1. Paus R, et al. *J Investig Dermatol Symp Proc.* 2018;19(1):S12-S17; 2. Azzawi S, et al. *Skin Appendage Disord.* 2018;4(4):236-244.

Immune Privilege

- Immune privilege protects the follicle from autoimmune attack[1]
- This process may be triggered by immunogenic alloantigen generated during anagen and exposed as a result of the apoptosis and necrosis associated with cyclical hair growth[1-4]



1. Pratt CH, et al. *Nat Rev Dis Primers.* 2017;3:17011; 2. Santos Z, et al. *Expert Opin Drug Discov.* 2015;10(3):269-292; 3. Tobin DJ. *Microsc Res Tech*. 1997;38(4):443-451; 4. Vogt A, et al. In: Hair Growth and Disorders. Springer. 2008:1-22.

Immune Cell Infiltration

- Loss of immune privilege allows immune cells to infiltrate the hair follicle, leading to an inflammatory swarm around the anagen hair bulb[1,2]

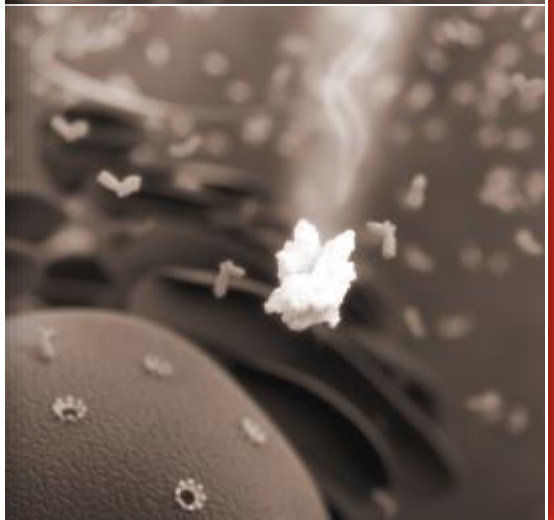
Hair bulb with immune privilege

Hair bulb with loss of immune privilege and inflammatory cytokine swarm

1. Azzawi S, et al. *Skin Appendage Disord.* 2018;4:236-244; 2. Bhat YJ, et al. *Hair Ther Transplant.* 2014;4:2.

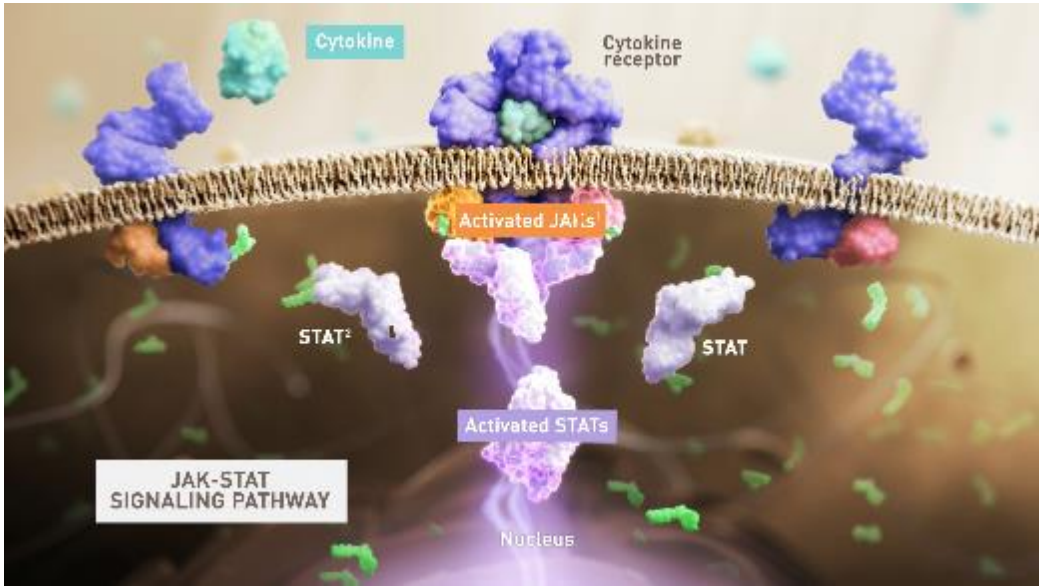
Chapter 3

The JAK-STAT Pathway in Alopecia Areata



The JAK-STAT Pathway

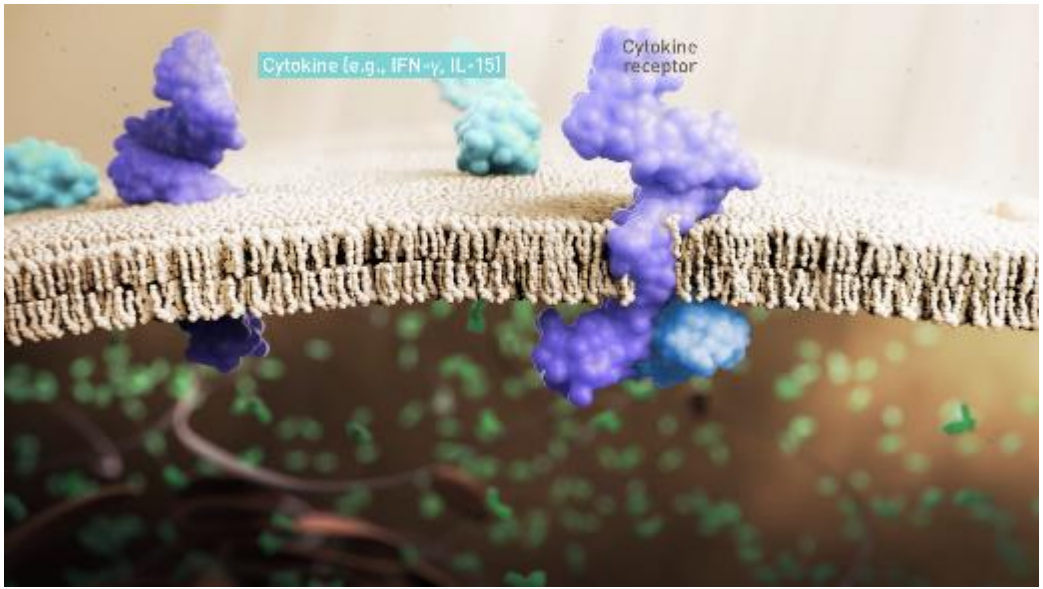
- The JAK-STAT pathway is a proinflammatory signaling pathway utilized by cytokines in AA[1,2]



1. Wang EHC, et al. *J Invest Dermatol*. 2018;138:1911-1916; 2. O'Shea JJ, et al. *Annu Rev Med*. 2015;66:311-328.

The JAK-STAT Pathway

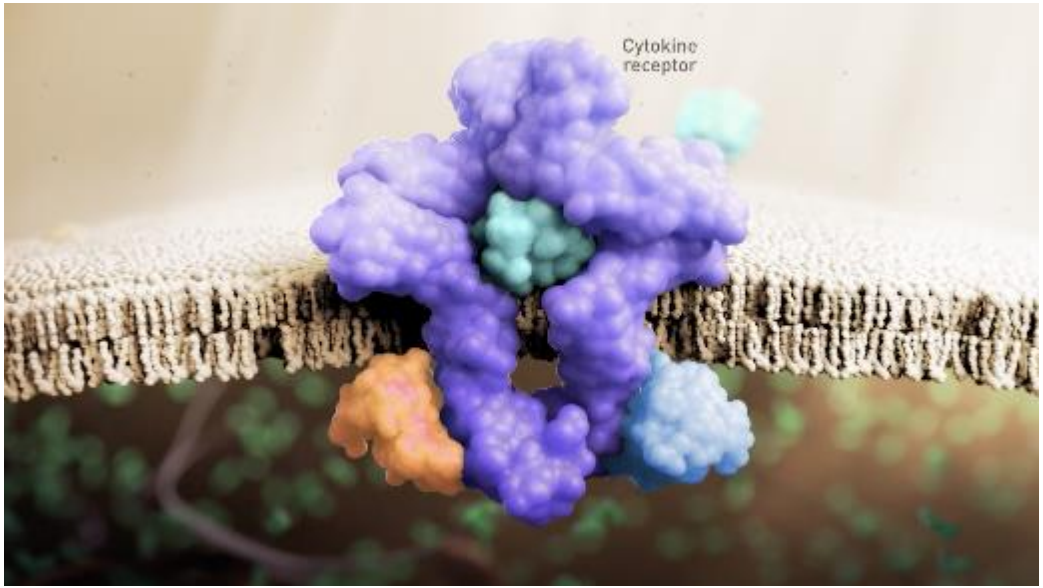
- The effects of cytokines such as IFN-γ and IL-15 are mediated by JAK kinases of the JAK-STAT pathway[1,2]



1. O'Shea JJ, et al. *Annu Rev Med*. 2015;66:311-328; 2. Wang EHC, et al. *J Invest Dermatol*. 2018;138:1911-1916.

The JAK-STAT Pathway

- The pathway is activated when ligand binding induces the dimerization of receptor subunits[1,2]



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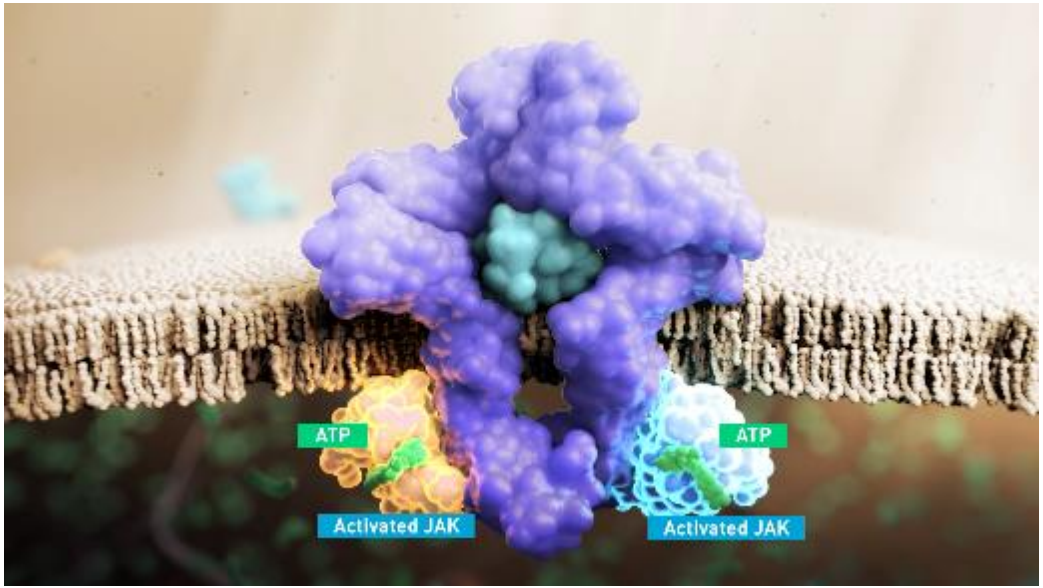
The JAK-STAT Pathway

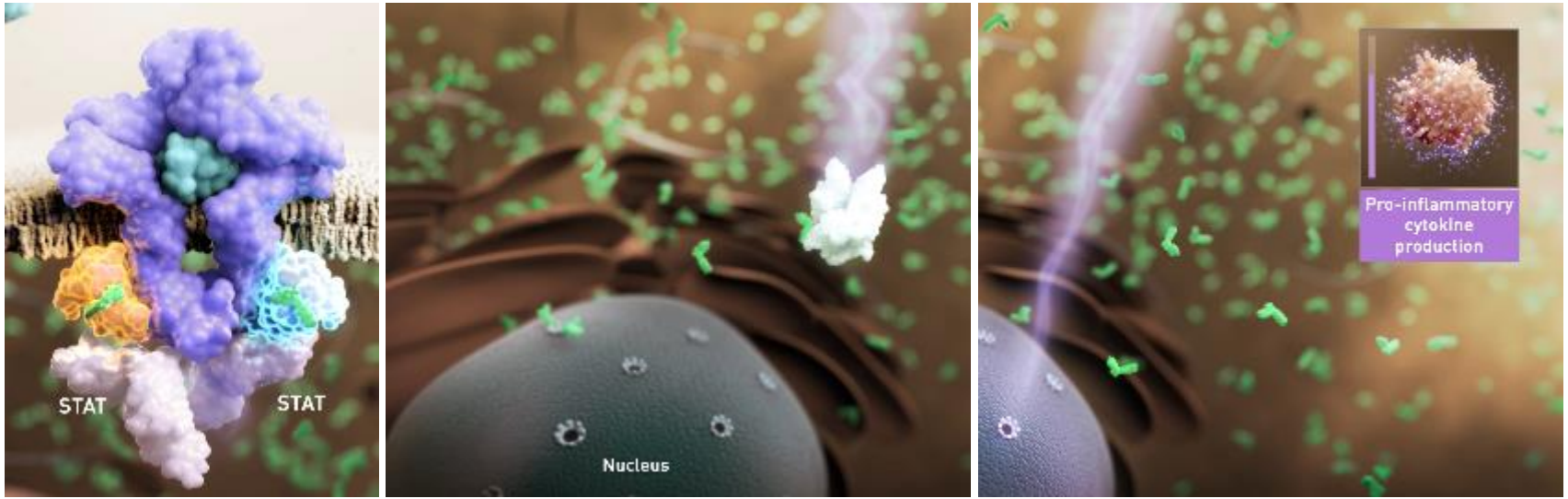
- Receptor-associated JAKs then bind ATP and become active[1]



1. O'Shea JJ, et al. *Annu Rev Med*. 2015;66:311-328.

The JAK-STAT Pathway

- Subsequent activation of STAT transcription factors, which translocate to the nucleus, regulate the transcription of genes involved in the production of proinflammatory cytokines responsible for disease maintenance in AA[1,2]



1. Wang EHC, et al. *J Invest Dermatol*. 2018;138:1911-1916; 2. O'Shea JJ, et al. *Annu Rev Med*. 2015;66:311-328.

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