

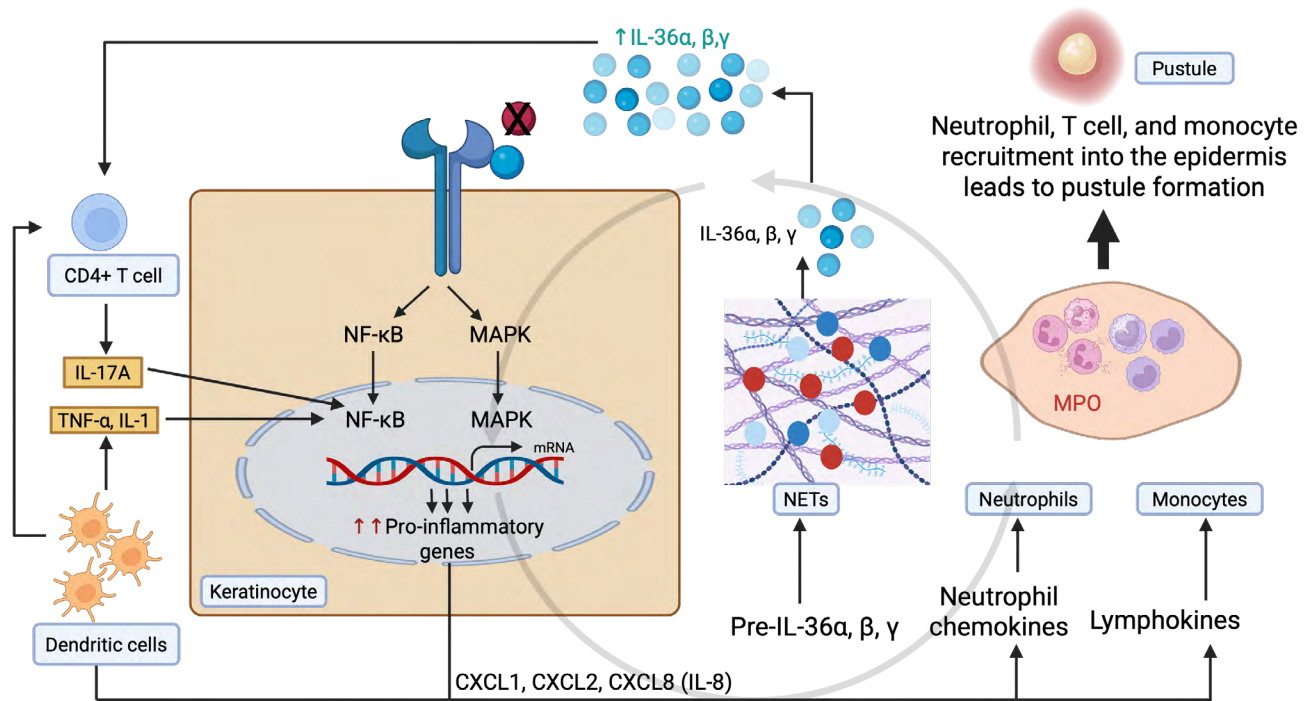
The IL-36 Connection: Immunology's Role in GPP Pathogenesis and Therapy



RAPID RECAP

Immunological Foundation of Generalized Pustular Psoriasis^{1,2}

- The International Psoriasis Council (IPC) defines GPP as a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules
- GPP lies on the autoimmune-autoinflammatory spectrum, with innate immunity/neutrophil-dominant features
- IL-36 dysregulation is central to GPP pathogenesis. The endogenous protein, IL-36 receptor agonist (IL-36Ra), normally restrains inflammatory signaling



⊗ mutant IL-36Ra; ● IL-36; ●● Neutrophil derived protease; NETs, neutrophil extracellular traps

- Unopposed IL-36 signaling creates a self-sustaining inflammatory loop with excessive neutrophil recruitment
- Gene variants contribute and influence onset, severity, and sex bias
 - **Loss of function:** *IL36RN, AP1S3, MPO, SERPINA3, BTN3A3*
 - **Gain of function:** *CARD14, MEFV*

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Diagnostic Criteria and Differentiation From Other Dermatoses^{1,2,3}

- **Essential criteria:** macroscopically visible sterile pustules on erythematous base and not restricted to the acral region or within psoriatic plaques
- **Histopathology:** spongiform pustules of Kogoj, dilated dermal vessels, and neutrophils
- **Comprehensive assessment:** history, physical exam, labs for inflammatory markers and metabolic abnormalities, biopsy, and genetic testing

Treatment Approaches^{4,5,6}

Traditional agents show variable and often inadequate efficacy

- **Systemic agents:** acitretin, cyclosporine, methotrexate
- **Biologics:** TNF- α , IL-17, IL-23 inhibitors

Targeted IL-36 receptor inhibitors

- **Spesolimab:** First FDA-approved GPP-specific therapy
 - Monoclonal antibody blocking IL-36R
 - Disrupts inflammatory amplification loop, reducing neutrophil and keratinocyte activation
 - Approved both to treat acute flares (900 mg, IV) and to prevent flares (300 mg, SC, every 4 weeks)
- **Imsidolimab:** emerging IL-36R inhibitor in Phase 3

GPP Management⁷

- **Control acute flares:** IV spesolimab; clinical/lab monitoring
- **Prevent/minimize future flares:** trigger management, genetic assessment, SC spesolimab maintenance
- **Optimize quality of life:** monitor using DLQI and provide supportive care

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Key Takeaways

- IL-36 axis is central to GPP pathogenesis
- Rapid recognition and differentiation from other pustular diseases is essential to initiate the right treatment
- IL-36R blockade can treat acute flares and prevent flare occurrence

References

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