

An 18-month-old boy is brought to the emergency department due to blood in his stool, which the parents noticed when changing his diaper. The infant has had no previous bleeding and has been eating and drinking normally. He has a history of recurrent otitis media, frequent herpes labialis, and 2 episodes of pneumonia. Vital signs are normal. On examination, the patient is well developed, well nourished, and has a fair complexion. He has eczema on his cheeks, trunk, and extremities. Scattered petechiae are also visible on his lower extremities. The remainder of the physical examination is unremarkable. Laboratory studies show a platelet count of  $24,000/\text{mm}^3$  and a leukocyte count of  $9,000/\text{mm}^3$ . Peripheral smear confirms the low platelet count and that the platelets are small. Genetic testing confirms the diagnosis. Which of the following processes is most likely affected by this patient's gene mutation?

- ☐ A. Antibody class switching
- ☐ B. Cytoskeleton regulation
- ☐ C. DNA repair
- ☐ D. Hydrogen peroxide production
- ☐ E. Maturation of T cells



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Explanation:

User Id: 

Wiskott-Aldrich syndrome	
<b>Etiology</b>	<ul style="list-style-type: none"><li>• X-linked recessive defect in WAS protein gene</li><li>• Impaired cytoskeleton changes in leukocytes, platelets</li></ul>
<b>Clinical features</b>	<ul style="list-style-type: none"><li>• Eczema</li><li>• Microthrombocytopenia (small platelets, low platelet count)</li><li>• Recurrent infections</li></ul>
<b>Treatment</b>	<ul style="list-style-type: none"><li>• Stem cell transplant</li></ul>

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This patient's **eczema** (itchy, red, scaly skin), **microthrombocytopenia** (small and low number of platelets), and **recurrent infections** are consistent with **Wiskott-Aldrich syndrome** (WAS). WAS is caused by an **X-linked recessive** defect in the **WAS** gene. This gene is primarily expressed in hematopoietic cells and regulates **cytoskeleton** remodeling in response to cell signaling. In WAS, the actin cytoskeleton in white blood cells is abnormal, resulting in immune dysfunction due to impaired cellular migration and immune synapse formation. Patients are at increased risk for recurrent bacterial, viral, and fungal infections.

Similarly, the cytoskeleton of platelets is also dysfunctional. Virtually all patients have significantly decreased platelet counts and size at the time of diagnosis. The resulting clinical findings can range from petechiae or purpura to severe bleeding such as intracranial hemorrhage, hematemesis, or hematochezia. In addition, autoimmune disorders (eg, eczema) occur in most patients with WAS. The treatment of WAS is **hematopoietic stem cell transplantation**.

**(Choice A)** T cell lymphocytes that lack CD40 ligand cannot bind to the CD40 receptor on B cells. Without CD40 activation, B cells cannot switch the antibody isotype they produce (eg, from IgM to IgG or IgA), resulting in hyper-IgM syndrome.



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**(Choice C)** Ataxia telangiectasia is a T cell deficiency associated with a defect in DNA repair. In addition to immune dysfunction, patients with ataxia telangiectasia experience progressive cerebellar degeneration and are at high risk for cancer.

**(Choice D)** Chronic granulomatous disease results from an inability of phagocytes to produce hydrogen peroxide in their lysosomes. Abscesses due to fungi or catalase-positive bacteria (eg, *Staphylococcus aureus*) are the characteristic feature.

**(Choice E)** Severe combined immunodeficiency (SCID) results from a severe T cell deficiency. A variety of gene defects can cause SCID and all prevent interleukin-7-driven maturation of T cells in the thymus. Patients with SCID have virtually no functional T cells; lack of T cells causes severe B cell dysfunction as well.

#### Educational objective:

Wiskott-Aldrich syndrome is an X-linked disorder characterized by the triad of thrombocytopenia, eczema, and recurrent infections. The thrombocytopenia is the most consistent feature and is characterized by a significant reduction in platelet volume and size.

#### References:

1. [Wiskott-Aldrich syndrome: diagnosis, current management, and emerging treatments.](#)
2. [WASP-WIP complex in the molecular pathogenesis of Wiskott-Aldrich syndrome.](#)