Mycophenolic Acid

Prelims: *Current events of national and international importance | Science & Technology*

Why in News?

A study reports that a fungus that causes pneumonia has become resistant to a drug never meant to kill it.

Mycophenolic Acid (MPA)

- **Origin -** A naturally occurring secondary metabolite originally isolated from ***Penicillium mold species.***
- **Clinical Role-** Functions as a potent **immunosuppressive agent** (administered commercially as Mycophenolate Mofetil or Mycophenolate Sodium).
- It is to prevent graft rejection in liver, kidney, and heart transplant recipients, and to treat severe autoimmune disorders (e.g., Lupus Nephritis).
- **Biochemical Mechanism**
  - Uncompetitively inhibits the enzyme Inosine-5'-monophosphate dehydrogenase (IMPDH).
  - IMPDH is the rate-limiting enzyme in the de novo synthesis of guanine nucleotides (essential building blocks for DNA and RNA replication).
  - Because T-lymphocytes and B-lymphocytes rely almost exclusively on the de novo pathway rather than the salvage pathway for purine synthesis, MPA selectively halts lymphocyte proliferation, dampening the immune response.

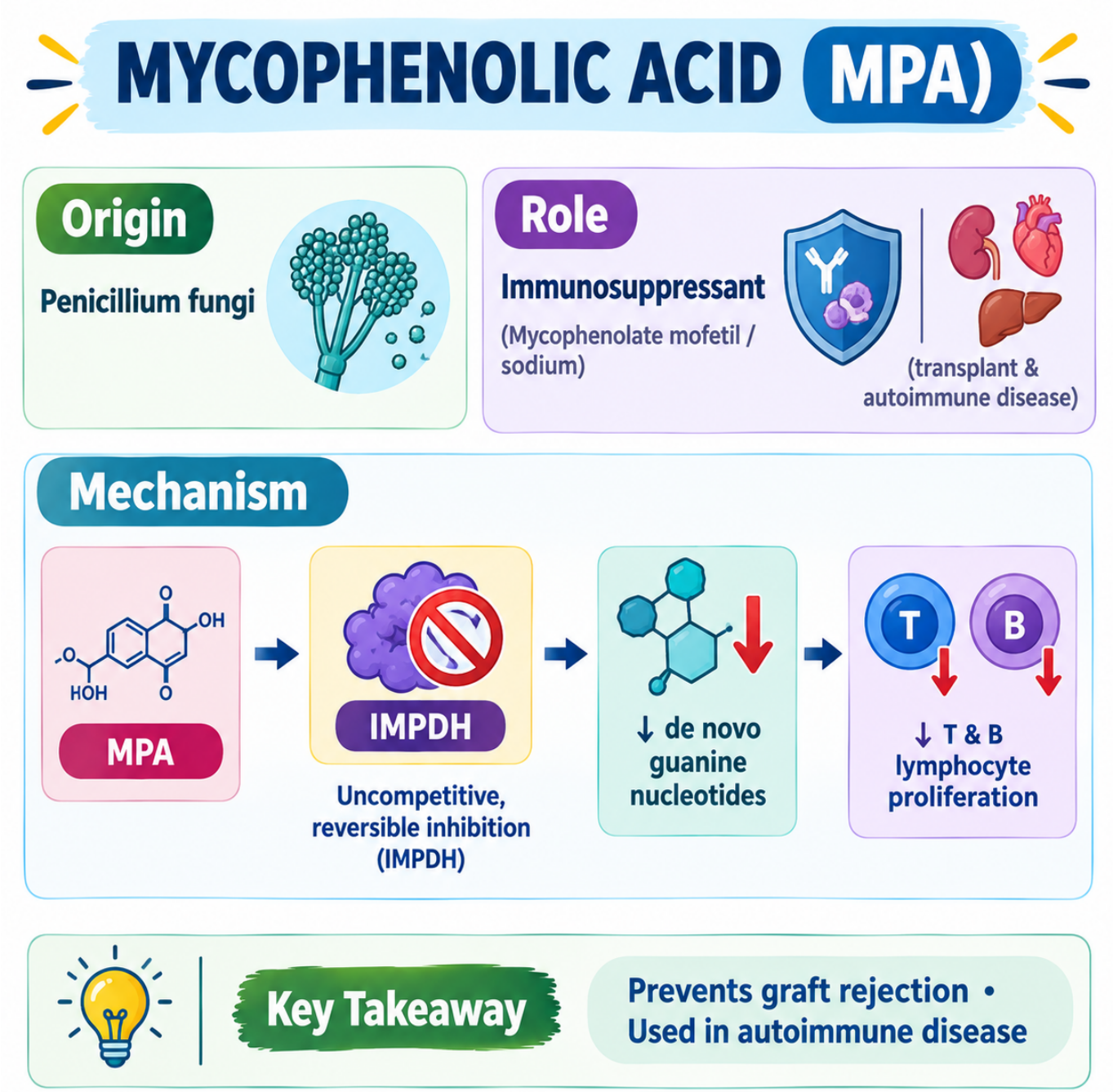
Mechanisms of Evolving Fungal Resistance

- **Target Overexpression & Mutation -** Up-regulation or genomic amplification of the *IMPDH* gene (*IMH1*), or specific point mutations in the binding pocket that prevent MPA from cropping while retaining catalytic function.
- **Efflux Pump Activation-** Up-regulation of ATP-Binding Cassette (ABC) transporters and Major Facilitator Superfamily (MFS) efflux pumps, which actively pump the drug out of the fungal cell cytoplasm.
- **Metabolic Degradation-** Production of specialized enzymes (e.g., glucuronosyltransferases or esterases) that chemically degrade or neutralize MPA before it reaches intracellular targets.

Significance

- Illustrates how natural biochemical warfare between soil microbes drives evolutionary arms races, leading to environmental resistance reservoirs long before drugs are deployed clinically.
- Transplant patients taking MPA are already severely immunosuppressed.
- The emergence of MPA-resistant fungal strains reduces therapeutic options for managing secondary fungal infections (such as *Aspergillosis* or *Candidiasis*).
- Highlights the evolutionary dilemma of using natural microbial products as human pharmaceuticals, as target organisms share millions of years of co-evolutionary history with

these compounds.



Reference

The Hindu | Fungus found evolving resistance to drug meant for humans

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