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Unit - III

TOPIC: MOLECULAR MEDICINE JAK-STAT SIGNALING IN ASTHMA

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MOLECULAR MEDICINE
JAK-STAT SIGNALING IN ASTHMA

What is JAK-STAT?

- The JAK-STAT(Janus kinase–signal transducer and activator of transcription) signaling pathway transmits information from chemical signals outside the cell, which causes DNA transcription and activity in the cell.
- The JAK-STAT system is a major signaling alternative to the second messenger system

COMPONENTS OF JAK-STAT

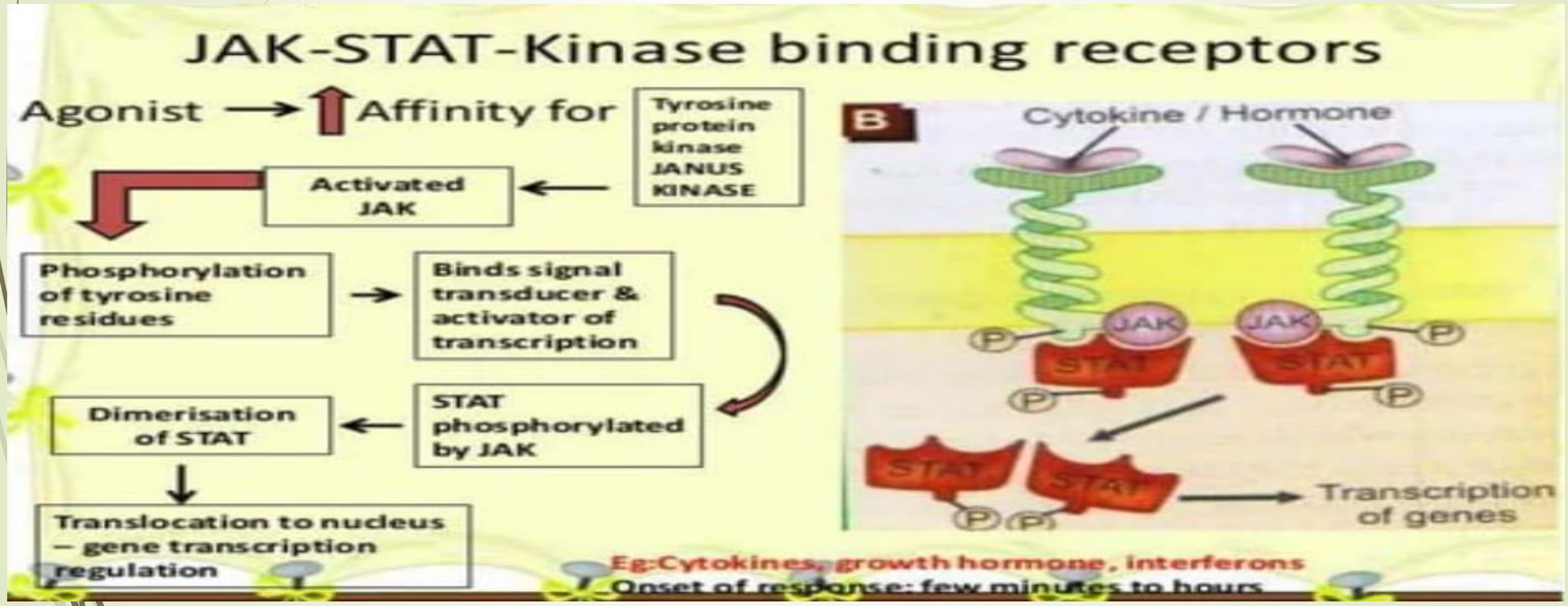
- A receptor
- Janus kinase(JAK) and
- Signal transducer and activator of Transcription (STAT).

MECHANISM OF JAK-STAT

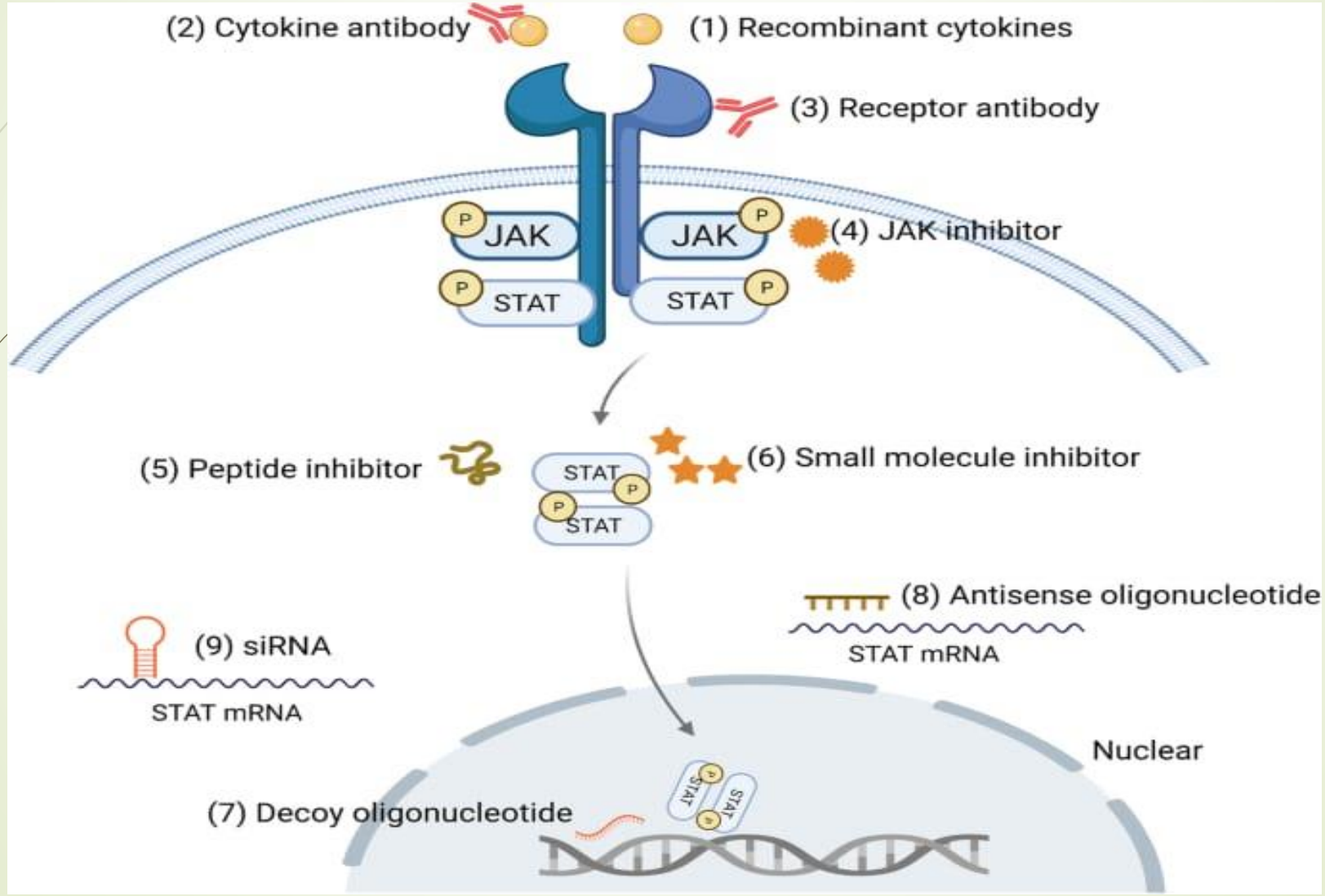
- JAKs, which have tyrosine kinase activity, bind to some cell surface cytokine receptors. The binding of the ligand to the receptor triggers activation of JAKs.
- With increased kinase activity, they phosphorylate tyrosine residues on the receptor STATs possessing SH2 domains are recruited to the receptors , and are themselves tyrosine-phosphorylated by JAKs. Activated STAT dimers accumulate in the cell nucleus and activate transcription of their target genes.

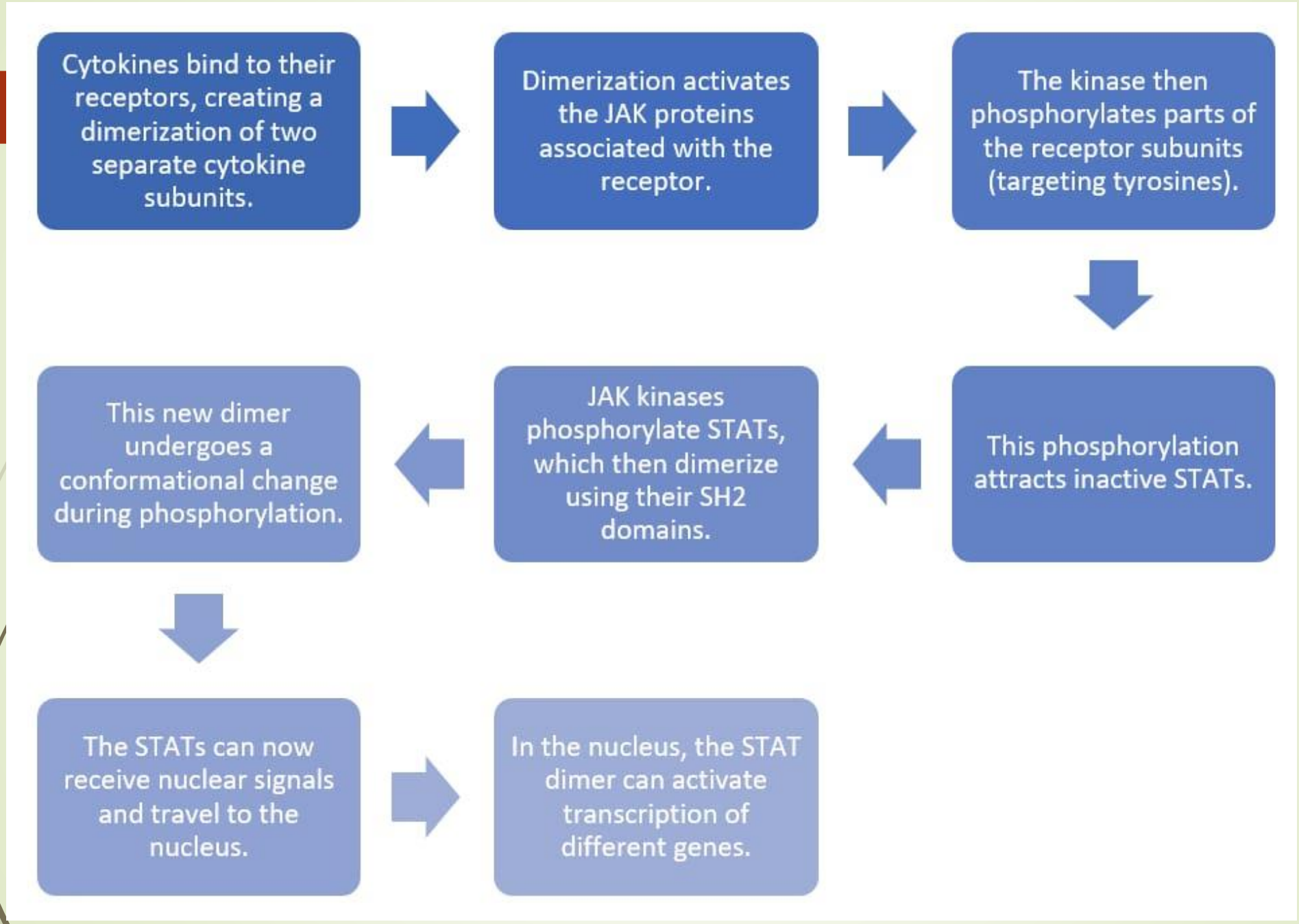
- STATs may also be tyrosine-phosphorylated directly by receptor tyrosine kinases, such as the epidermal growth factor receptor, as well as by non-receptor tyrosine kinases such as c-src.

HOW PATHWAY WORKS



JAK-STAT PATHWAY




Cytokines bind to their receptors, creating a dimerization of two separate cytokine subunits.
Dimerization activates the JAK proteins associated with the receptor.
The kinase then phosphorylates parts of the receptor subunits (targeting tyrosines).
This phosphorylation attracts inactive STATs.
JAK kinases phosphorylate STATs, which then dimerize using their SH2 domains.
This new dimer undergoes a conformational change during phosphorylation.
The STATs can now receive nuclear signals and travel to the nucleus.
In the nucleus, the STAT dimer can activate transcription of different genes.

The pathway is negatively regulated on multiple levels. Protein tyrosine phosphatases remove phosphates from cytokine receptors and activated STATs.

- Suppressors of cytokine signalling (SOCS) inhibit STAT phosphorylation.
- Protein inhibitors of activated STAT (PIAS), which also act in the nucleus through several mechanisms.
- For example, PIAS1 and PIAS3 inhibit transcriptional activation by STAT1 and STAT3 respectively by binding and blocking access to the DNA sequences they recognize.

Effects on Airway Inflammation

- **Mucus Production**: Activation of STAT6 by IL-4 and IL-13 leads to increased mucus production by airway epithelial cells, which contributes to airway obstruction.
- **Airway Hyperreactivity**: The inflammatory mediators and cytokines that are regulated by JAK-STAT signaling can lead to increased airway hyperreactivity, a hallmark of asthma.
- **Airway Remodeling**: Chronic inflammation driven by JAK-STAT signaling can result in structural changes in the airways, such as increased collagen deposition and smooth muscle hypertrophy.

Therapeutic Implications

JAK Inhibitors: Drugs that inhibit JAKs (e.g., tofacitinib) have been investigated for their potential to reduce inflammation in asthma by blocking the signalling of multiple cytokines.Anti-IL-4/IL-13 Therapies: Monoclonal antibodies that target IL-4 or IL-13, such as dupilumab, directly interfere with the JAK-STAT6 signalling pathway and are already used in clinical practice to treat severe asthma.

SUMMARY

The JAK-STAT signaling pathway is a key player in the inflammatory and immune responses seen in asthma. Targeting this pathway offers a promising approach to managing the disease, particularly in severe cases that are resistant to conventional therapies.

REFERENCE

- Hu, X., li, J., Fu, M. *et al.* The JAK/STAT signalling pathway: from bench to clinic. *Sig Transduct Target Ther* **6**, 402 (2021). https://doi.org/10.1038/s41392-021-00791-1
- Steve N. Georas *et al*. (2021). JAK inhibitors for asthma. Volume 148, Issue 04, October 2021, Pages 953-963
- Seyyed Shamsadin Athari. (2019). Targeting cell signaling in allergic asthma. 4, 45. https://doi.org/10.1038/s41392-019-0079-0

Thank you