Immune modulation in Down syndrome and COVID-19

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What do Down syndrome and COVID19 have in common?

Can the study of Down syndrome help us understand COVID19 and vice versa?

Both conditions involve ‘hyperinflammation’

Similar immune-modulatory strategies could potentially benefit both, individuals with Down syndrome and COVID19 patients
What is a cytokine storm?

A cytokine storm refers to an over-reaction of the immune system, leading to high levels of inflammatory proteins known as ‘cytokines’

This overload of cytokines can damage organs such as the lung, heart, kidneys and liver, eventually leading to organ failure.

The cytokine storm caused by the SARS-CoV-2 virus is associated with the severity of COVID19 symptoms.
Cytokine storms during lung viral infections

Lung epithelial cells are ‘first responders’, producing ‘primary cytokines’ such as Type I and III Interferons (IFNs).

A first wave of immune activation involves immune cells known as macrophages and dendritic cells (DCs), which produce other primary cytokines, such as IL-6, TNF-α, and IL-1β.

A second wave of immune activation involves additional immune cells, such as NK cells and various types of T cells (CD8, helpers, Tregs), which in turn produce yet more cytokines, such as IFN-γ, IL-10, and others.

Eventually, dozens of cytokines are induced.
Trisomy 21 activates the Interferon response

People with Down syndrome show a hyperactive ‘Interferon response’

The Interferon response is a key aspect of the immune system that ‘interferes’ with viral infections

The Interferon response acts throughout the entire human body

Without an Interferon response, we would probably die within days of a common viral infection

Too much Interferon response is known to cause autoimmunity which is more common in Down syndrome

People with Down syndrome are ‘fighting off’ viruses 24/7, even when there is no virus present
Trisomy 21 activates the Interferon response

4 of the 6 IFN receptors are encoded on chr21!!

Human chromosome 21

People with Down syndrome show a hyperactive interferon response
Hyperinflammation is associated with both COVID-19 severity and trisomy 21

Cytokine measurements

COVID19 patients

Healthy individuals with trisomy 21

The cytokines associated with high risk of COVID19 are elevated in Down syndrome

Healthy individuals with Down syndrome display a ‘mild cytokine storm’
Is Interferon hyperactivity good or bad during COVID19 in Down syndrome?: It’s bad

Increased IFN activity is likely to cause stronger cytokine storms, with increased risk of downstream pathology.

Espinosa JM, Cell Reports Medicine 2020
Is there a way to tone down the hyperinflammation observed in both COVID19 and Down syndrome?
Three types of IFN signaling

All three types of IFN signaling employ ‘JAK kinases’ for signal transduction.

JAK1 is required for all three types of IFN signaling.
### FDA-approved JAK inhibitors
tone down the Interferon response

<table>
<thead>
<tr>
<th>Company</th>
<th>Marketed Name</th>
<th>Target</th>
<th>Indication</th>
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<tr>
<td>Lilly</td>
<td>Olumiant® baricitinib</td>
<td>JAK1&amp;2</td>
<td>Rheumatoid arthritis (2018)</td>
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<tr>
<td>abbvie</td>
<td>RINVOQ® pasodacitinib</td>
<td>JAK1</td>
<td>Rheumatoid arthritis (2019)</td>
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Also tested in clinical trials for:

- Alopecia areata
- Atopic dermatitis
- Depression
- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Leukemia
- Psoriasis
- Vitiligo
Using JAK inhibitors to treat alopecia areata in Down syndrome

Rachubinski et al, JADRC 2019
The first clinical trial for JAK inhibition in Down syndrome

- For immune-driven skin conditions:
  - Atopic dermatitis
  - Alopecia areata
  - Hidradenitis suppurativa
  - Psoriasis
  - Vitiligo

- Treated with the JAK inhibitor Tofacitinib for 4 months
- Safety as the primary endpoint
- While also monitoring:
  - Markers of immune dysregulation in the blood
  - Impacts on other autoimmune conditions
  - Impacts on cognition and quality of life
JAK inhibition in COVID-19

Several clinical trials, including NIAID’s ACTT, are now testing JAK inhibition in COVID-19.
Conclusions

Individuals with Down syndrome display immune dysregulation that could increase the risk of developing more severe symptoms during COVID19.

Toning down the immune system can have therapeutic benefits in both Down syndrome and COVID19.

Individuals with Down syndrome and COVID19 should be monitored more closely for signs of hyperinflammation.

Individuals with Down syndrome should be included in ongoing clinical trials testing the safety and efficacy of JAK inhibitors and other immune-modulatory strategies in COVID19.
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