From *immune senescence and insulin resistance* to *obesity and sarcopenia*: iNKT cell as bridge?

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CONCLUSION

The physiological process of ageing is characterized by an increase in visceral fat, insulin resistance, immune senescence and sarcopenia. We hypothesize that iNKT cells, a regulatory type of T-cells, play an important role in this ageing process. The arguments supporting this hypothesis are given here. Moreover, chemical and biological characterization of known iNKT activators is presented by a clustering dendrogram. This allows us to more efficiently design novel activators with biased immune-modulating properties and to investigate their effect on muscle mass and function. As such, our findings will contribute to an improved pathophysiological understanding of sarcopenia from an immunological point of view with diagnostic and therapeutic clinical applications.

KEY PLAYERS

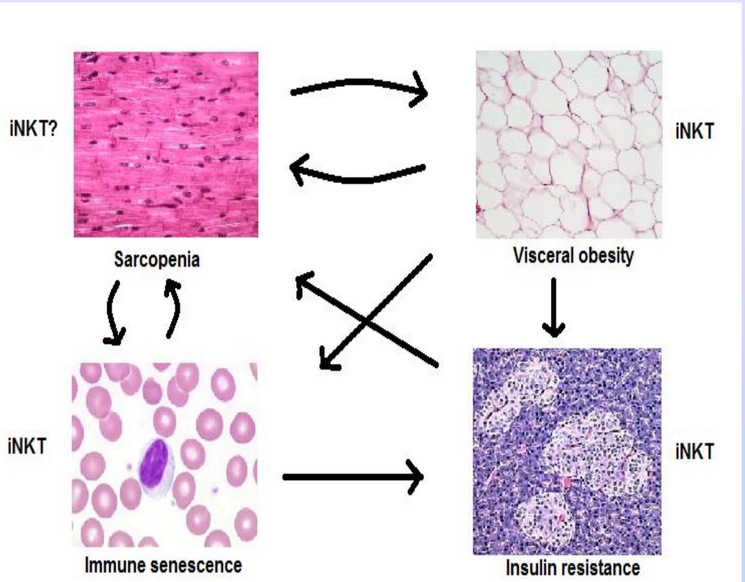

Figure 1. Visercal obesity, insulin resistance, immune senescence and sarcopenia: strongly associated processes. iNKT cells play an important role in the first 3 processes. We speculate that also in sarcopenia, iNKT cells are crucial in the pathophysiology.

iNKT IN AGEING PROCESSES

1. Visceral fat and iNKT

Recent data points to an important crosstalk between visceral fat and iNKT cells:

- ✓ iNKT cells are **present in adipose tissue**, both in mice and men.
- ✓ iNKT cells become **activated** by adipocytes and dietary lipid excess.
- ✓ iNKT **knock-out mice** have a changed adiposity and adipose tissue inflammation.

2. Insulin resistance and iNKT

The well-known link between obesity and insulin resistance is (partly) mediated via iNKT cells:

- ✓ evidence for **functional crosstalk** between adipocytes and iNKT cells (see above).
- ✓ iNKT **knock-out mice** can suppress insulin resistance in early-stage obesity.

3. Immune senescence and iNKT

Ageing is associated with a dysregulation of the immune system: basal low-grade inflammation (inflammaging) as well as impaired activation when stimulated. iNKT cells are known to participate in this immune senescence:

- ✓ the quantity of iNKT cells **declines** with ageing in human blood and liver.
- ✓ there is an **increase** of iNKT cells with ageing in spleen and lymph nodes.
- ✓ iNKT cells from aged mice have a different **cytokine-profile** in response to infection compared with young iNKT cells.

4. Sarcopenia and iNKT

Sarcopenia is strongly related to visceral obesity, insulin resistance and immune senescence:

- ✓ lipotoxicity and adipokines lead to a declined **proteïn synthesis** in muscle cells.
- ✓ non-diabetic obese rats develop **resistance** to insulin's anti-proteolytic actions compared to non-diabetic lean rats.
- ✓ **myokines**, *e.g.* IL-15, may play a role in immune senescence, more specific the NK cell dysregulation.
- ✓ TNFα and IL-6, **pro-inflammatory cytokines**, augment with ageing, negatively affecting muscle tissue.

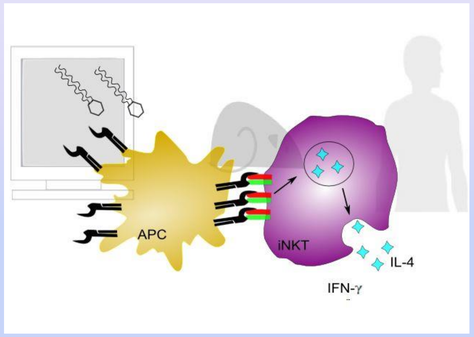

Figure 2. Interaction of APC with iNKT.

iNKT cells in a flash

• T-cells with a restricted/semi-invariant TCR: Vα14-Jα18 in mice and Vα24-Jα18 in human.
• Recognize glycolipid antigens on the MHC I-like molecule CD1d, presented by APC's.
• High and rapid cytokine production on activation.
• α-GalCer glycolipid is the prototype of strong iNKT activators.
• Modified glycolipids can strongly bias the cytokine-profile.
• They play a role in auto-immune diseases, infections and cancer .

MODULATING iNKT RESPONSE

1 + 2 + 3 + 4

=> Hypothesis: iNKT cells play an important role in sarcopenia

=> modulating iNKT responses will influence the disease progression.

We need **strong iNKT activators** that elicit a **specific biased immune-response**. To support this search, the physico-chemical and biological properties of the currently known iNKT activators were investigated. With a **computational *in-silico* approach**, we characterized these iNKT activators in order to fuse these two information-sets.

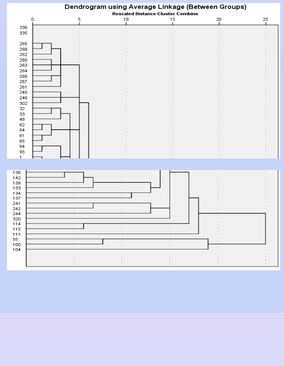

Figure 3. An illustration of the physico-chemical hierarchical cluster analysis (HCA) analysis of the currently known iNKT activators.

References

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