Oefentherapie tijdens & na kanker:

Immuuntherapie 2.0

de Berekuyl academy

GÖTEBORGS UNIVERSITET

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PAIN IN MOTION oncology

www.paininmotion.be

Immuuntherapie voor kanker: Nobelprijs 2018

Hoe kunnen wij als kinesitherapeut de immuniteit van patiënten met/na kanker beïnvloeden?

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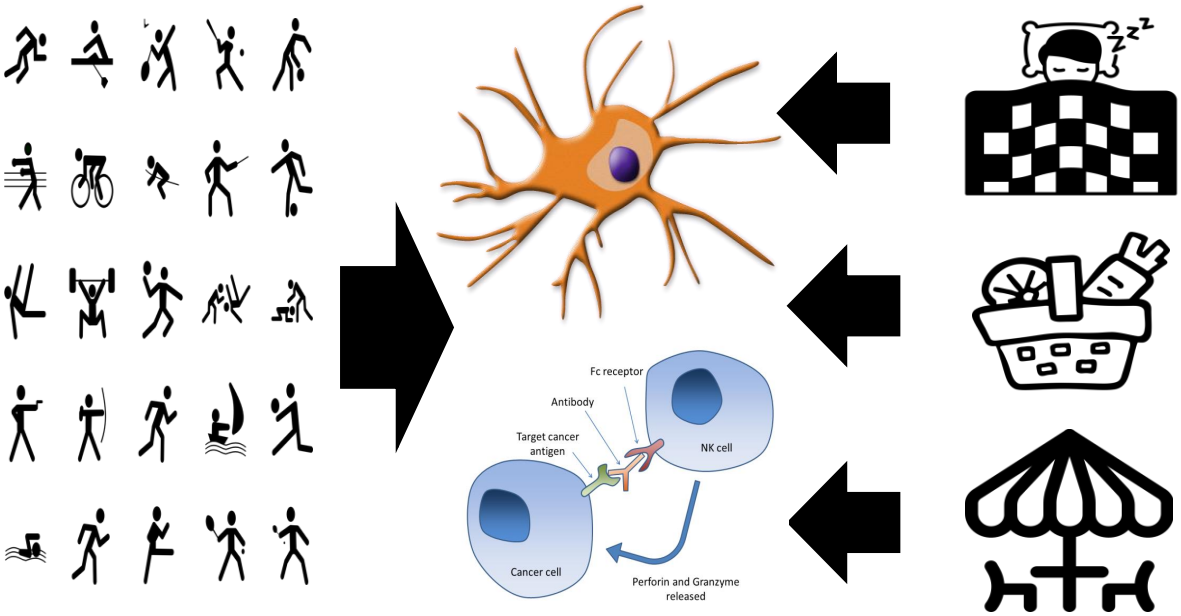


Cancer treatment depresses immune function

Radiotherapy
Chemotherapy
Surgery

→

natural killer cell function↓
T cell function↓
monocyte phagocytosis↓

If exercise is not capable of treating or preventing cancer (recurrence), at least it is important for (restoring) normal body functioning, including immune functioning.

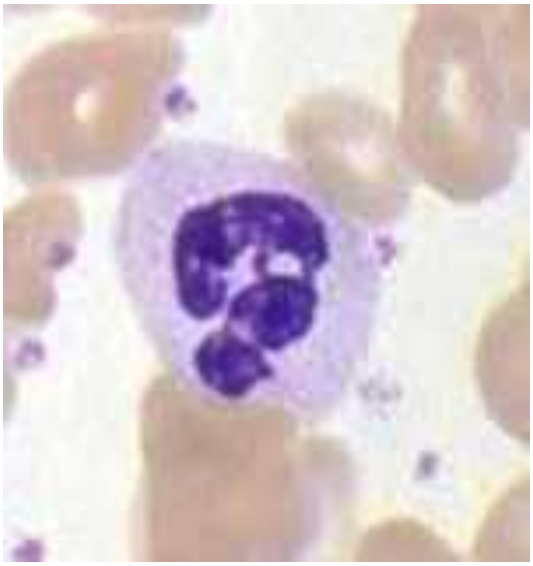
Inhoud

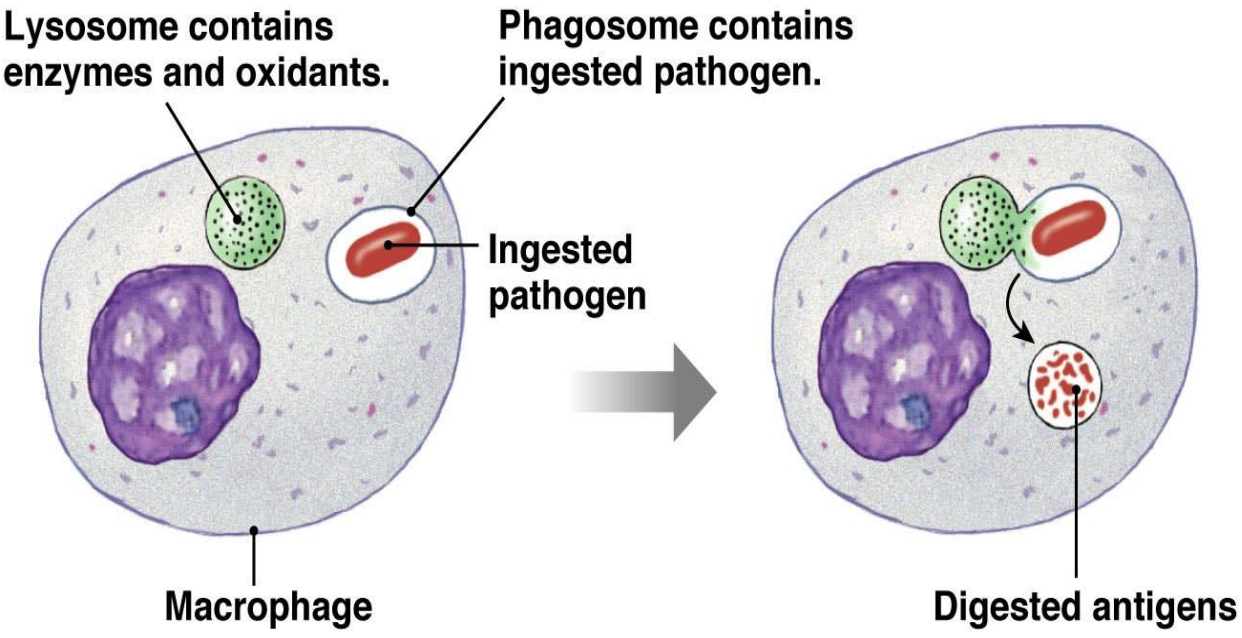
1. Oefentherapie als immuuntherapie voor kanker
2. Voeding als immuuntherapie voor kanker

Goals

1. Learning how **exercise** can influence the immune system
2. Understanding the close **interaction** between exercise & the immune system (i.e. inflammation, neutrophils, NK cells and dendritic cells)
3. Identifying ways of '**treating**' the immune system through exercise therapy in cancer patients and cancer survivors

Neutrophils are first-line defenders against cancer by nature of their phagocytic and cytolytic properties





Neutrophils & exercise: acute effects

→ $[neutrophils]_{blood}$ ↑↑

→ expression complement receptors on neutrophils↑

→ activity (phagocytosis) neutrophils↑↑

→ oxidative burst (ROS↑)

→ elastase → proteolysis elastine

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Neutrophils & exercise: training effects

Long-term high intensity training

→ neutrophil function (oxidative burst & phagocytosis)↓, at rest & during exercise

= adaptation of the human body to counter post-exercise muscle soreness?

Moderate training → no suppression of neutrophil function

Exercise & inflammation

Pedersen & Saltin. *Scand J Med Sci Sports* 2006 - Woods et al. *Neurol Clin* 2006

Exercise
→ acute **pro**-inflammatory

Exercise training long-term **anti**-inflammatory effects in:
- healthy people
- chronic heart disease
- metabolic syndrome
- rheumatoid arthritis → safe to use strength training (no immune activation)

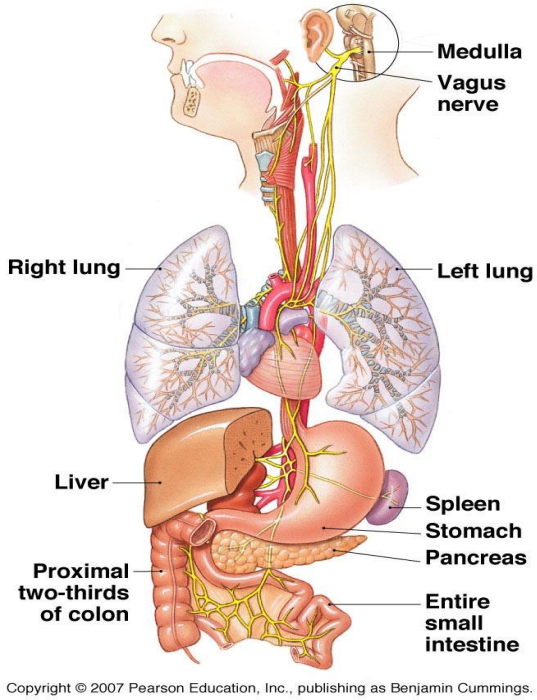
Inflammation & cancer

Cancer prevention:

inflammation activates killer cells & cellular immunity: ++

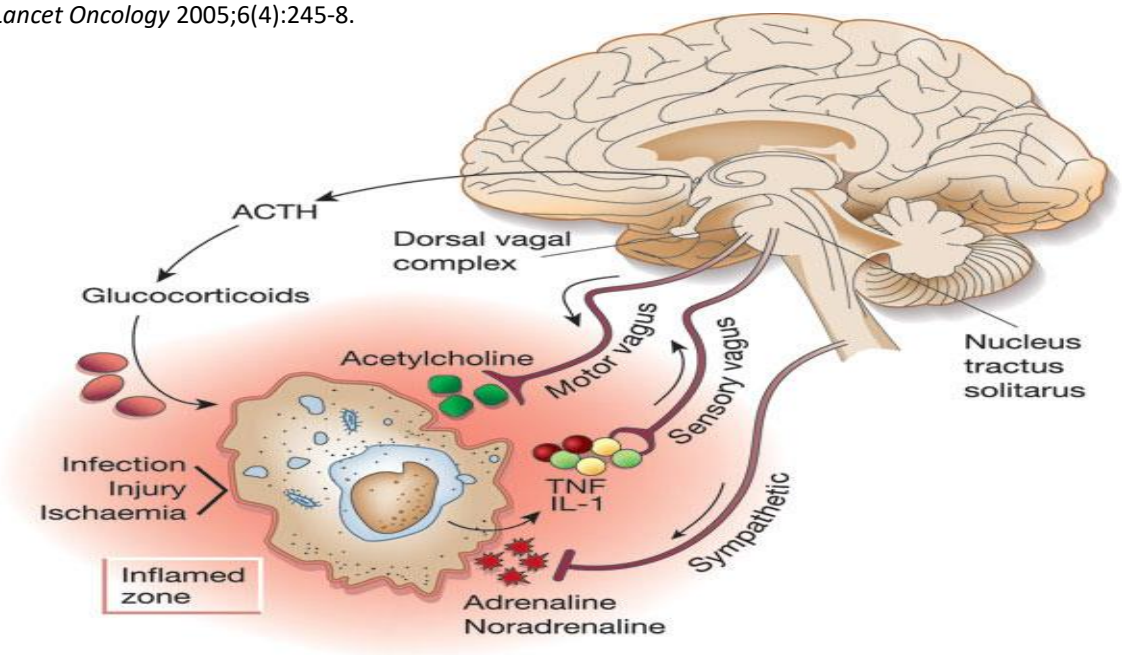
chronic inflammation should be prevented: --

Cancer: inflammation has a role in metastasis: - -



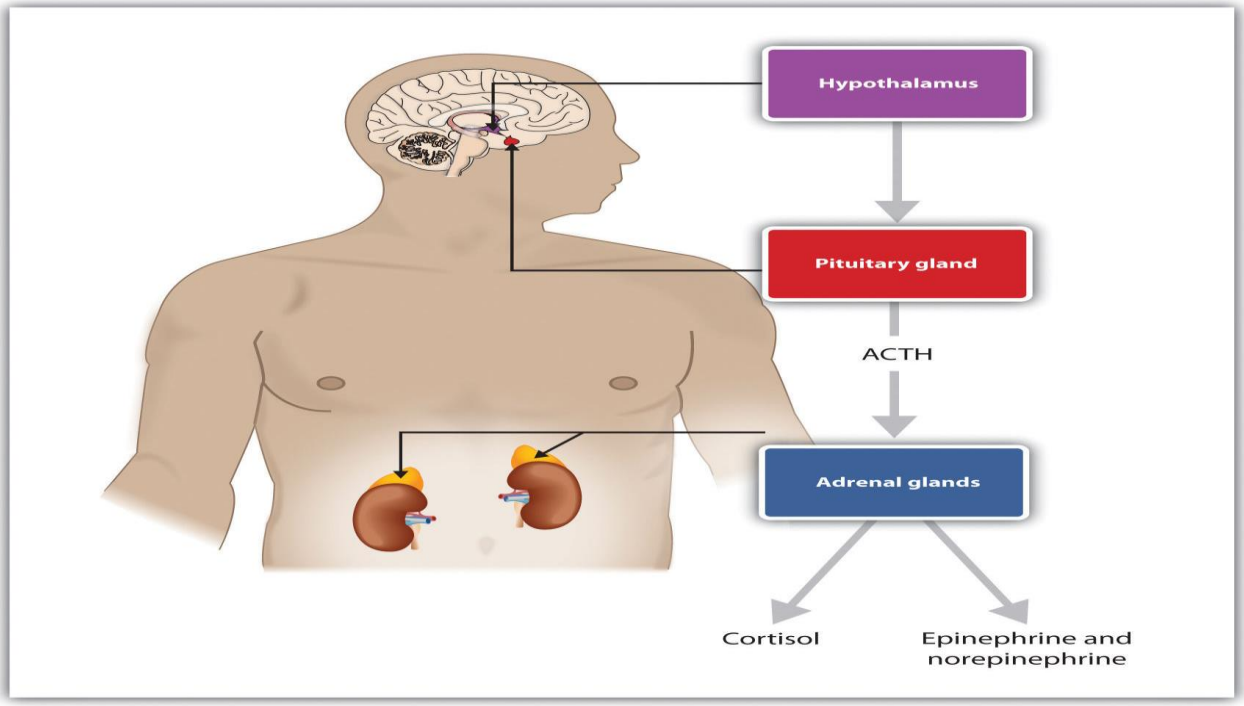
Nervus vagus (X) as most important para-sympathetic nerve

Gidron Y. et al. **Does the vagus nerve inform the brain about preclinical tumours and modulate them?** *Lancet Oncology* 2005;6(4):245-8.



Overall, results from studies conducted with cancer patients and survivors support the hypothesis that **inflammatory processes contribute to fatigue** during and particularly after treatment. The association between inflammation and fatigue has been documented primarily in breast cancer survivors, though similar effects have been observed in ovarian and testicular cancer survivors.

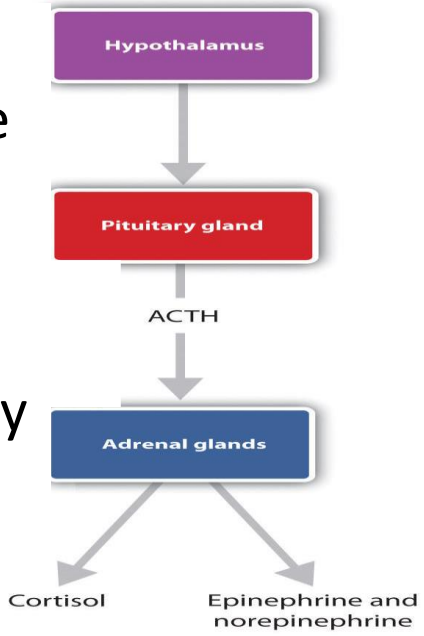
Bower JE. *Nat Rev Clin Oncol* 2014; 11(10):597-609.



Cancer survivors:

- Blunted corstisol response to psychological stress
- Flatter diurnal cortisol rhythm
- Lower heart rate variability

Porter et al. 2003, Bower et al. 2005
Croswell et al. 2015, Caro-Moran et al. 2015



Exercise & Inflammation:
An Optimal Stress Response System is Required

White & Castellano. *Sports Medicine* 2008

Exercise

→ glucocorticoids↑ + catecholamines↑

→ **inhibition pro**-inflammatory cytokines (IL-12, TNF-α, IFN-γ)

→ **stimulation anti**-inflammatory cytokines (IL-4, IL-10, TGFβ)

= **delayed anti-inflammatory response**

Stressmanagement = PREHABILITATION in breast cancer

Stressmanagement training before breast cancer surgery → reducing anxiety, depression & fatigue in acute postoperative period + **positive impact on immune system**

Tsimopoulou et al. *Ann Surg Oncol* 2015;22:4117-4123.
Mina et al. *PM&R* 2017;9:S305-S316.

The Role of Exercise in Cancer

Cancer Prevention

Cancer Treatment

Prevention of Recurrence

Treatment of Post-Cancer Fatigue and Pain

Exercise Therapy & Cancer: Evidence

lack of exercise: major **risk factors** for all cancer mortality

regular moderate-intensity exercise → **30-50%↓ in mortality** in breast & colorectal cancer

direct **antioncogenic effects** on disease progression

immune function↗ in cancer survivors
(NK-cells, monocytes, neutrophils)

Exercise immunology & cancer

neutrophils
inflammation

cytotoxic cells (including NK cells)

dendritic cells

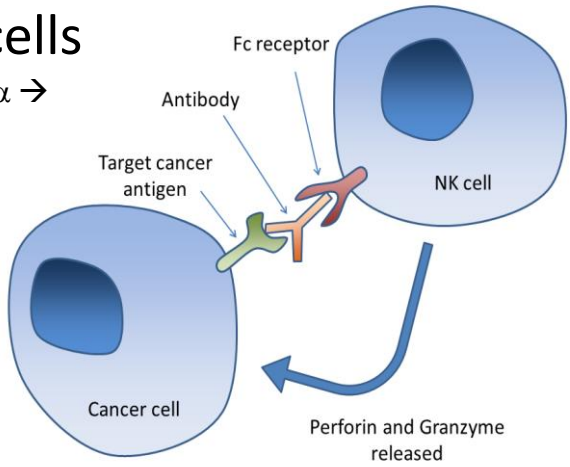
Cytotoxic cells
(cytotoxic T cells, NK cells, monocytes/macrophages)

recognize & kill tumour cells

e.g. NK cells produce tumour necrosis factor α → tumour cell apoptosis

cancer prevention

limit or prevent tumour spread (metastasis)



NK cells & cancer

tumour cells escape from NK-cells

depressed cytotoxicity NK-cells

decreased number

NK cells play a key regulatory role in the generation of dendritic cell-induced antitumor immunity

Lion et al. *Oncologist* 2012

antitumor immunotherapies via cytokines, antibodies

Langers et al. *Biologics* 2012

Nitric oxide & NK-cells

chemotherapy → NO↑

high levels of NO → NK cytotoxicity↓

oxidative stress → NK cytotoxicity↓ & fatigue↑

Exercise Effects on NK-cells as Anti-Cancer Medicine: Current Evidence

Animals:

Exercise-dependent NK cell infiltration in tumors **controls tumor growth**

Humans:

Exercise stimulates NK cell mobilization

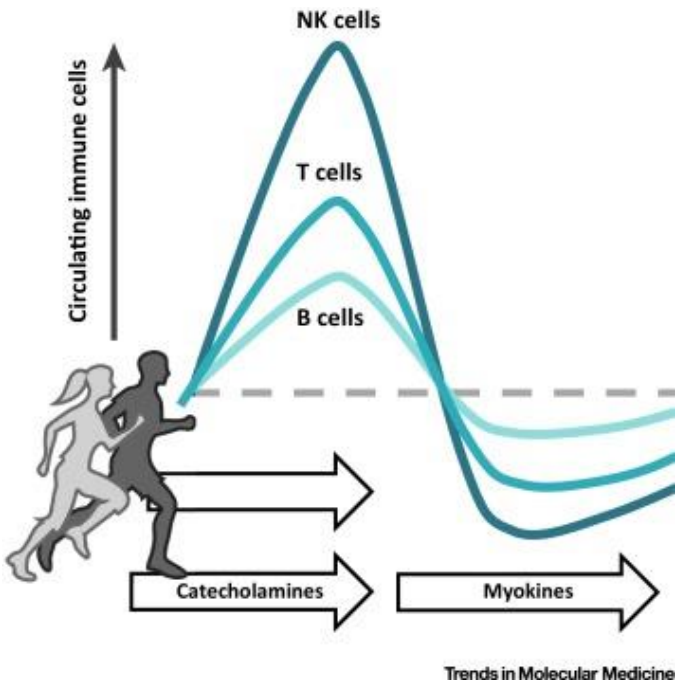
Exercise-induced **NK cell infiltration in tumors** → control of tumor growth? Needs to be verified in cancer patients

Use **high intensity exercise** to obtain specific control of tumor growth through NK cell mobilization

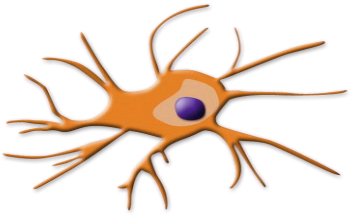
Idorn & Hojman. *Trends in Molecular Medicine* 2016;22(7):565-577.

Mobilization of (stored) immune cells during exercise

Idorn & Hojman. Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends in Molecular Medicine* 2016;22(7):565-577.



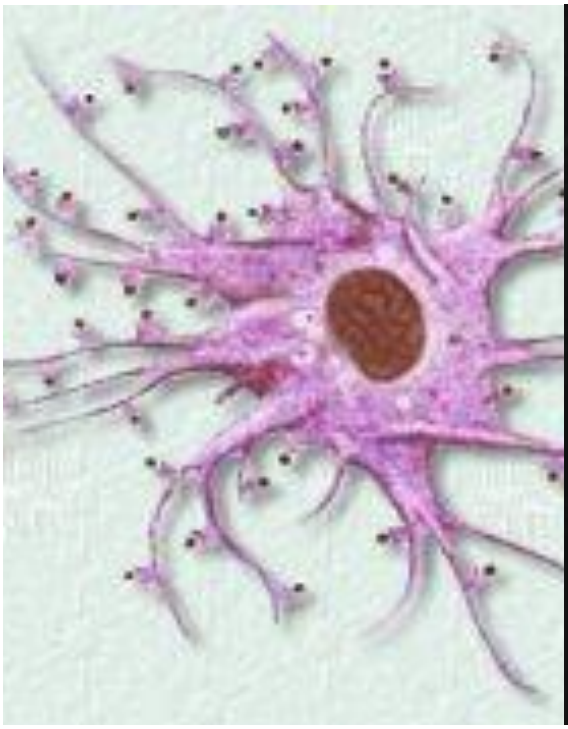
Dendritic cells

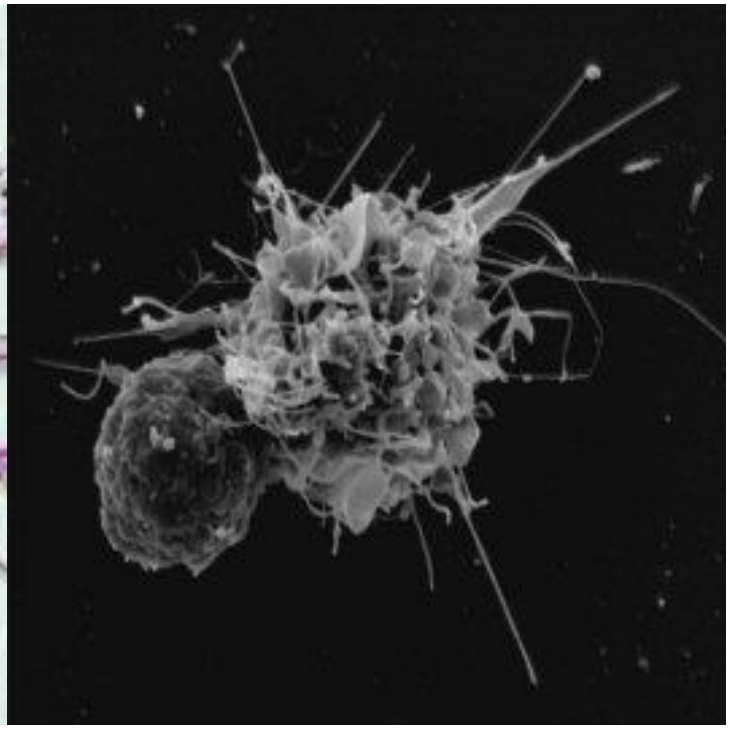


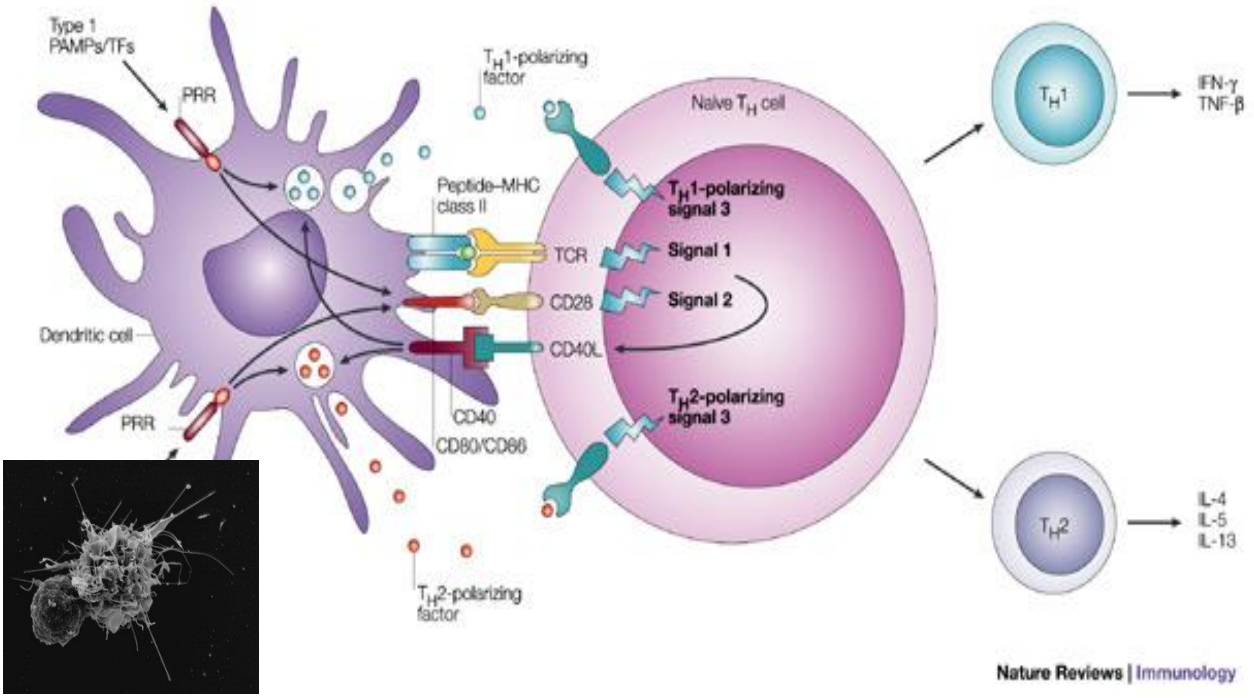
ingest pathogens or debris from apoptotic or necrotic cells

→ present antigen to lymphocytes

infiltrate in tumours → antitumour immune responses





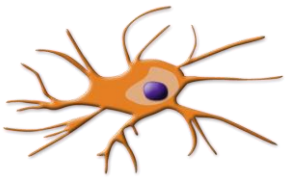

Type 1
PAMPs/TFs
PRR
T_H1-polarizing factor
Naive T_H cell
Peptide–MHC class II
TCR
CD28
CD40L
CD40
CD80/CD86
Dendritic cell
PRR
T_H1-polarizing signal 3
Signal 1
Signal 2
T_H2-polarizing signal 3
T_H2-polarizing factor
T_H1
IFN-γ
TNF-β
T_H2
IL-4
IL-5
IL-13
Nature Reviews | Immunology

Dendritic cells & exercise in healthy people

15–20 min of moderate intensity exercise → dendritic cells in blood↑↑

20 min at 80% $\dot{V}O_{2\ MAX}$ → dendritic cells in blood↑↑

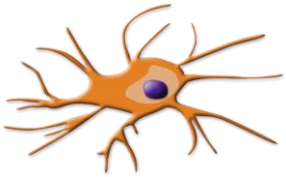
marathon → some types of dendiritic cells in blood↑, others↓



Brown et al. *Physiology & Behaviour* 2018;194(1):191-198.

Nickel et al. *Eur J Appl Physiol* 2012;112(5): 1699-1708.

Dendritic cells & cancer



Antitumour immune response of dendritic cells:

- tumour antigen presentation to T-cells in lymph nodes
- IFN-α↑, IL-12↑ → prevention of T-cell apoptosis → T-cell survival
- direct lysis, apoptosis & cell cycle arrest of cancer cells
- number of dentritic cells in (peri)tumoural area ~ survival prognosis

How translating these findings to clinical practice?

Exercise therapy in internal disorders: How maintaining immune health?

Walsh et al. *Exercise Immunology Reviews* 2011

Start with a programme of **low to moderate volume & intensity**

Employ a **gradual** and periodised **increase** in training volumes & loads

Add **variety** to limit training monotony & stress

Exercise should be **fun**, not a burden

Avoid excessively heavy training loads that could lead to **exhaustion**

Exercise therapy in internal disorders: How maintaining immune health?

Walsh et al. *Exercise Immunology Reviews* 2011

Ensure sufficient rest & **recovery**: recovery activities immediately after training

Increase frequency of shorter training sessions rather than enduring fewer but longer sessions

Employ shorter sharper (spike) sessions mixed with lower intensity work

Exercise therapy in internal disorders: How maintaining immune health?

Walsh et al. *Exercise Immunology Reviews* 2011

Graded exercise: **reduce size of increments** in training frequency, volume, intensity & load e.g. increases of 5-10% per week rather than 15-30%

Particular attention to nutritional strategies

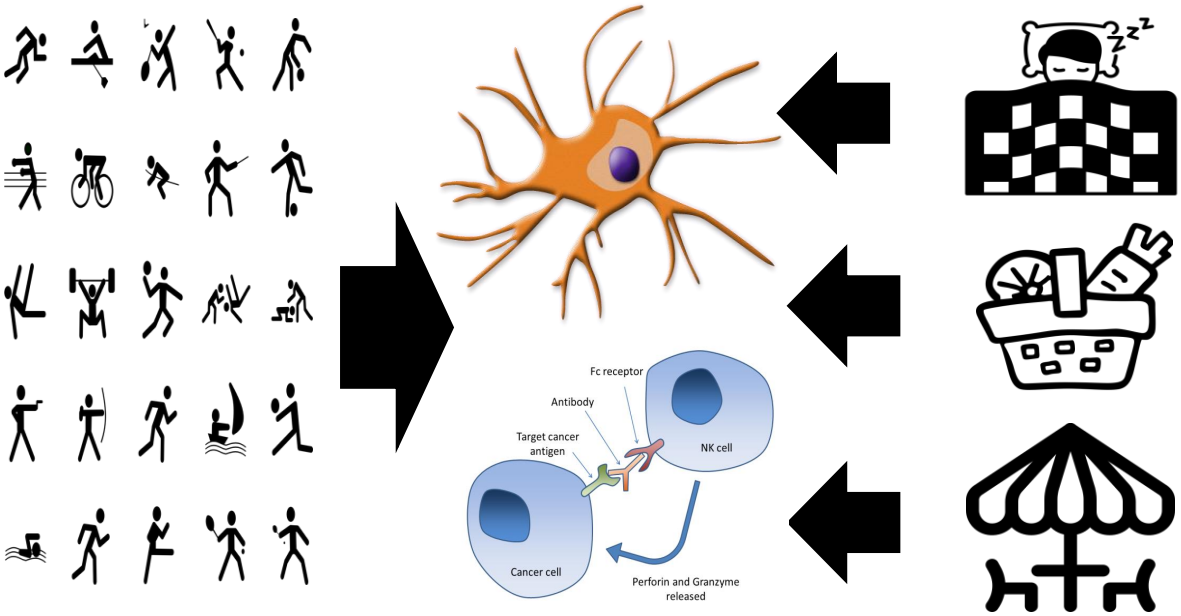
Sleep quality!

Goals achieved?

1. How does exercise influence the immune system?

2. How does your understanding of the close interaction between exercise & the immune system impact upon your treatment of cancer patients and **cancer survivors**?

3. Identifying ways of '**treating**' the immune system through exercise therapy in cancer patients and cancer survivors



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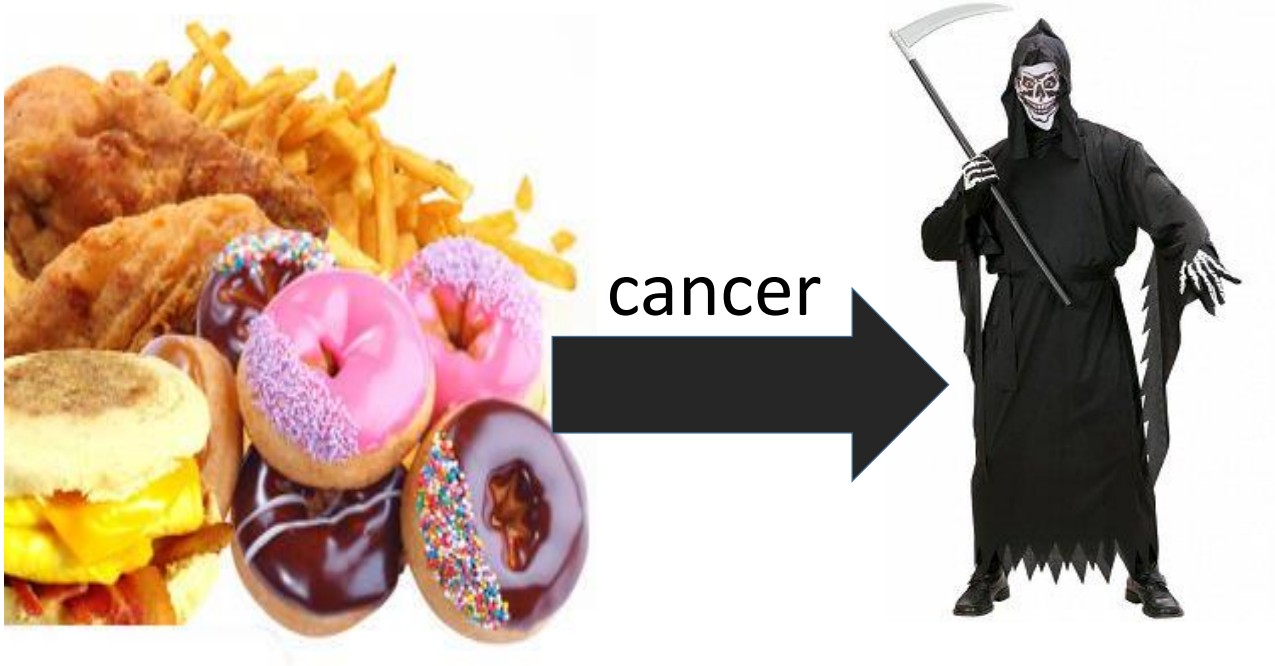
Goals

1. Learning **which diets** can influence the immune system

2. Understanding the close **interaction** between diet, nutrition & the immune system

3. Identifying ways of '**treating**' the immune system through diet

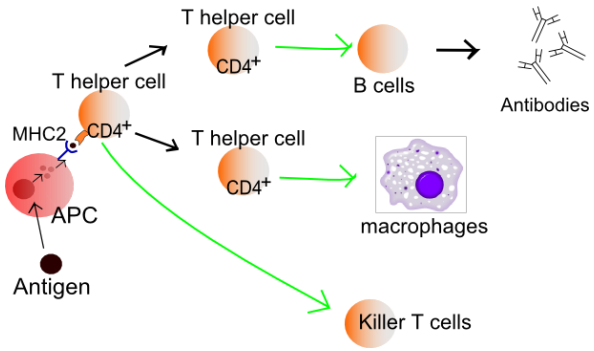


aging ↑

cancer

overnutrition → aging ↑

?



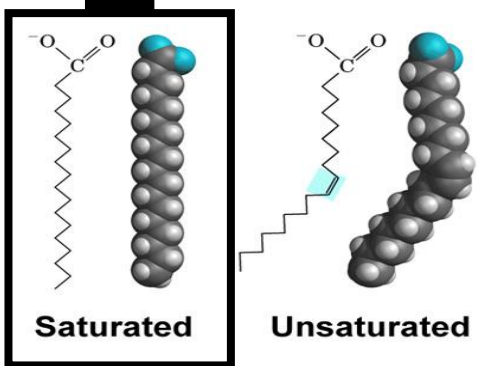
?

aging ↓ ← caloric restriction

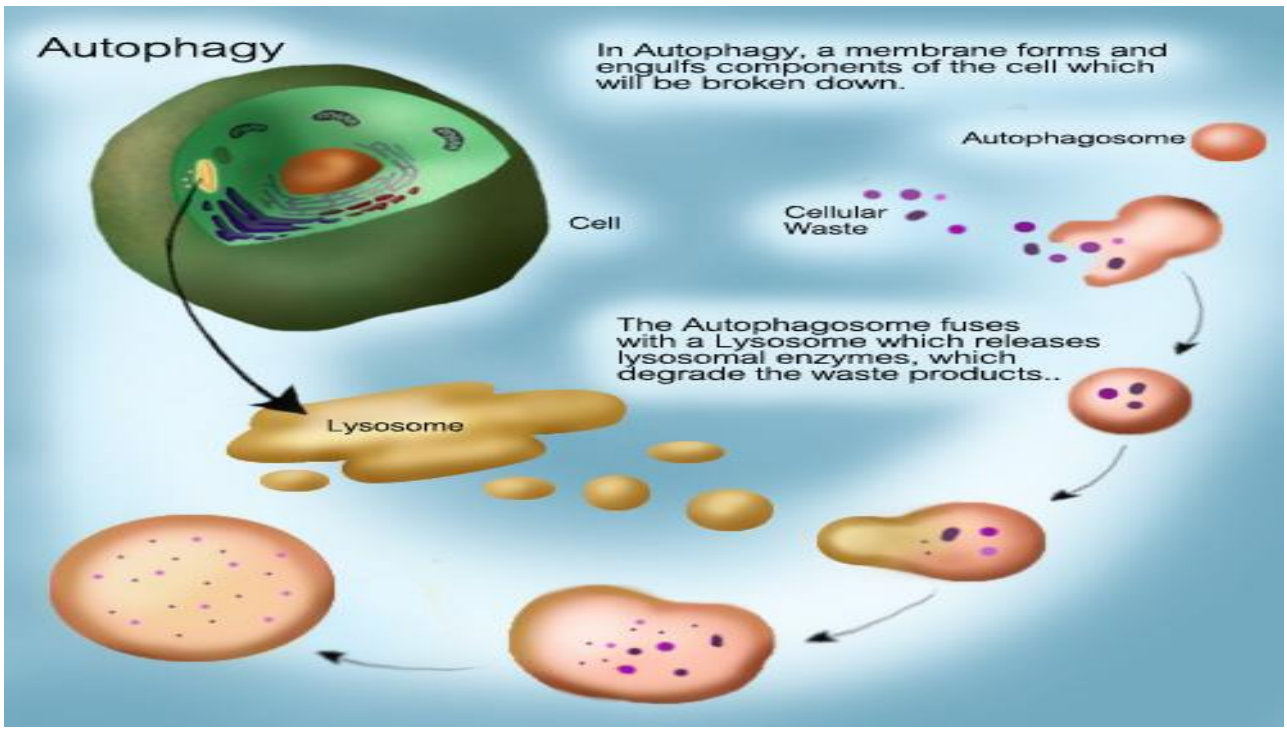
chronic inflammation → cancer

chronic inflammation

IL-1β↑, IL-6↑, TNF-α↑



autophagy inhibition



Autophagy = bying new furniture

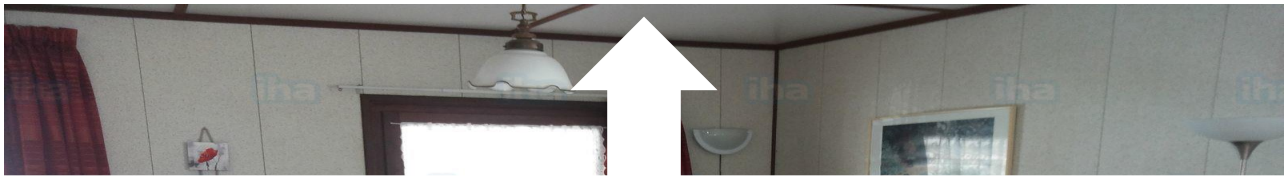
autophagy inhibition

cytoplasmatic recyclying damaged organelles↓ → aging↑

autophagy inhibition

accumulating of oncogenic products → cancer

Autophagy = bying new furniture



FASTING or caloric restriction

Anti-inflammatory effect

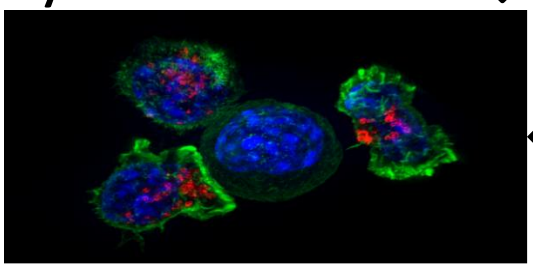
chronic inflammation
incl. sustained STAT3
& NF-ƙB signalling

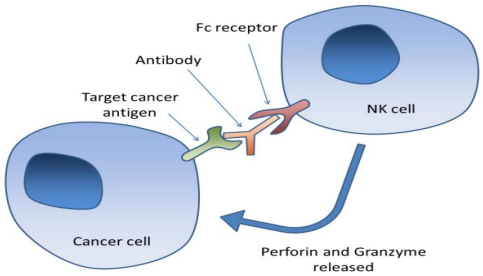
apoptosis
suppression
cancer (development, growth & spreading)

Pro-inflammatory	Anti-inflammatory
Overnutrition	Fasting
Overweight / obesity	Ketogenic diet
Proteins	Caloric restriction
Saturated fatty acids	Vitamin B6
Grain (gluten)	Vitamin D3
Red meat	Beans – vegetables
Smoking	Coffee
Hyperglycemia	Nuts (omega-3 fatty acids)

There is more to it than inflammation

cytotoxic T-cells↓





Natural Killer-cells↓ dendritic cell function↓

Alternative ways of affecting cancer risk through diet

IGF-I↑ → cancer risk↑

VEGF↑ → tumour growth

Insulin, IGF-I & IGF-II: anti-apoptotic effect

Alternative ways of affecting cancer risk through diet

→ IGF-I↑ → cancer risk↑

Calorie-restricted diets
Protein-restricted diets
Fasting regimes
Physical activity

→ IGF-I↓ → cancer risk↓

Immunology backs-up lifestyle guidelines for cancer prevention and cancer survivors

healthy weight
physically active
eat more wholegrains, vegetables, fruits & legumes (such as beans)
avoid sugary drinks
limit fast foods
limit red meat
avoid processed foods
avoid alcohol
do not use supplements

World Cancer Research Fund/American Institute for Cancer Research. *Diet, nutrition, physical activity and cancer: a global perspective.* Continuous Update Project Expert Report. Available for free at dietandcancerreport.org

References & further reading

Zitvogel L, Pietrocola F, Kroemer G.
Nutrition, inflammation and cancer.
Nature Immunology 2017;18(8):843-850.

World Cancer Research Fund/American Institute for Cancer Research.
Diet, nutrition, physical activity and cancer: a global perspective.
Continuous Update Project Expert Report.
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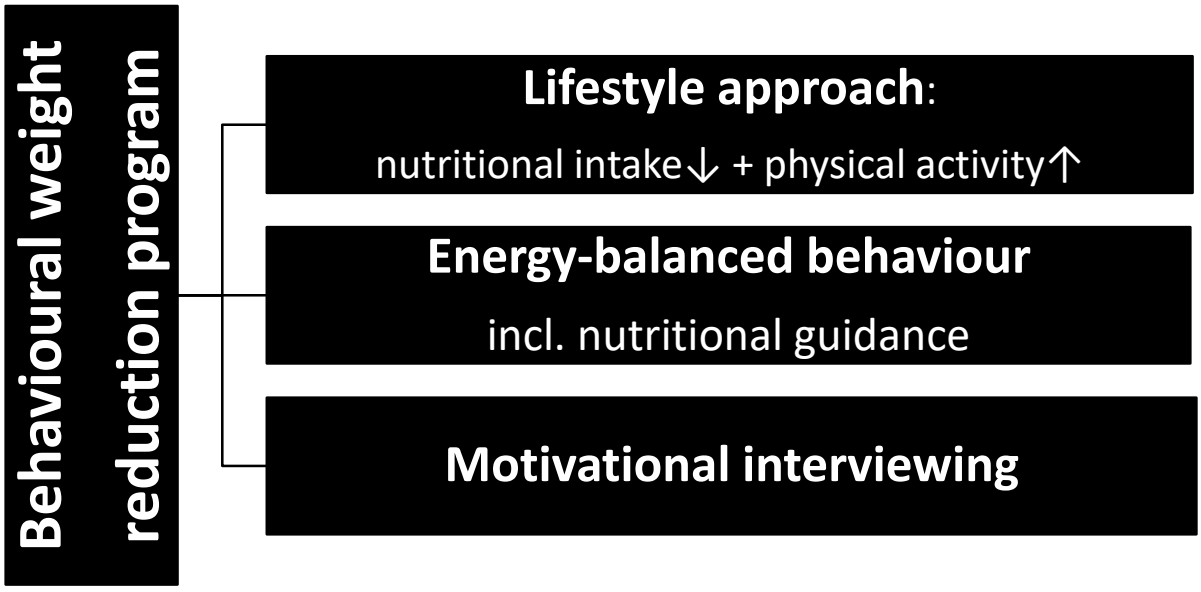

Caloric restriction in breast cancer? *Timing is everything*

PAIN IN MOTION

BMI relates to persistent pain after breast cancer surgery
Ding et al. *Oncotarget.* 2017;8(26):43332-43343.

Pre-surgical caloric restriction affects tumor biology in primary breast cancer
Demark-Wahnefried et al. *International journal of cancer.* 2020;146(10):2784-2796.

Preconditioning dietary interventions in cancer populations may be better timed after surgical resection

Goals achieved?

1. **Which diets** can influence the immune system?

2. Understanding the close interaction between diet, nutrition & the immune system: **how** can diet affect the immune system?

3. Can you think of ways of '**treating**' the immune system through diet?

The Cancer Diet

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