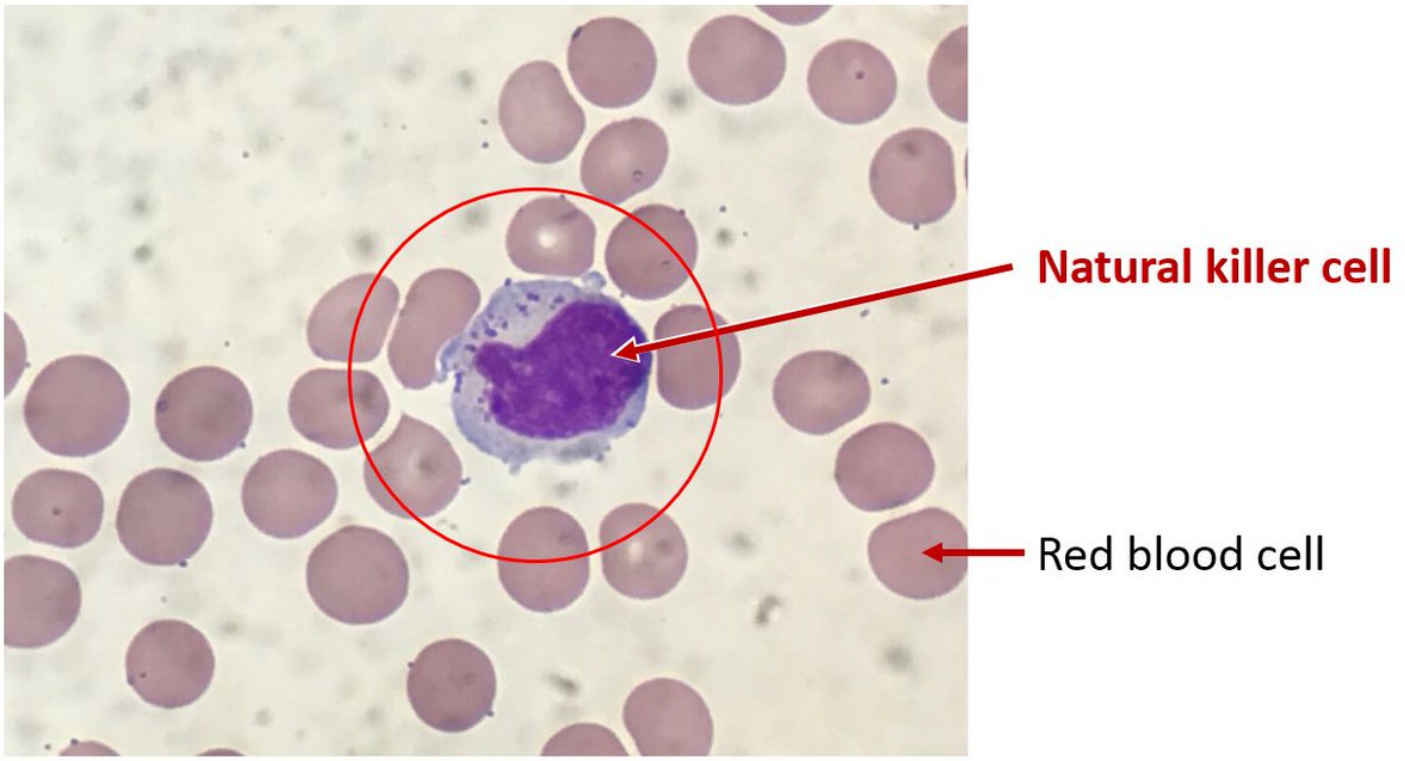
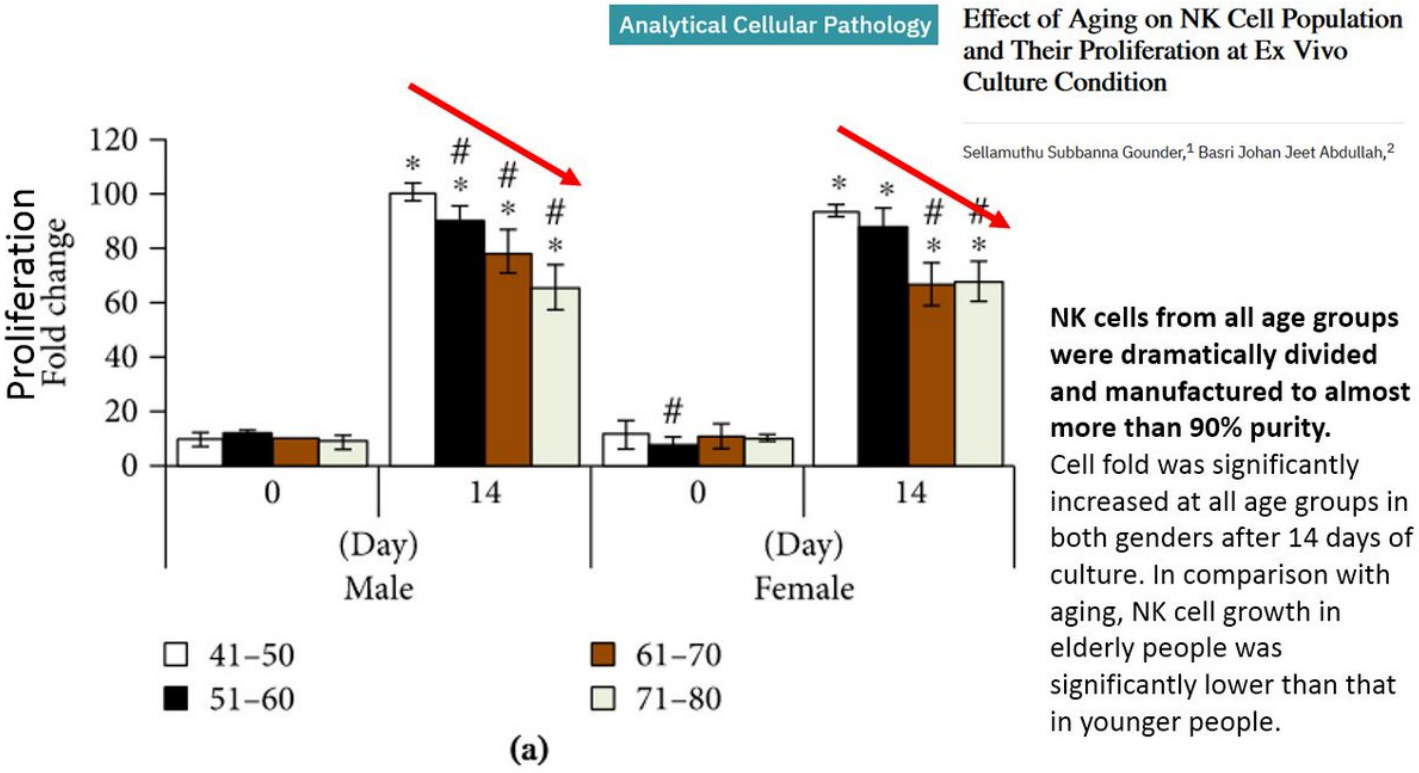
Twitter Thread by Dr John B.

Dr John B.
@DrJohnB2

(1/n) The important role of natural killer (NK) cells in COVID-19.
A summary of key insights:
- NK cells are cytotoxic lymphocytes & part of the innate immune system
- They play an important role in virus infection control & immunomodulation

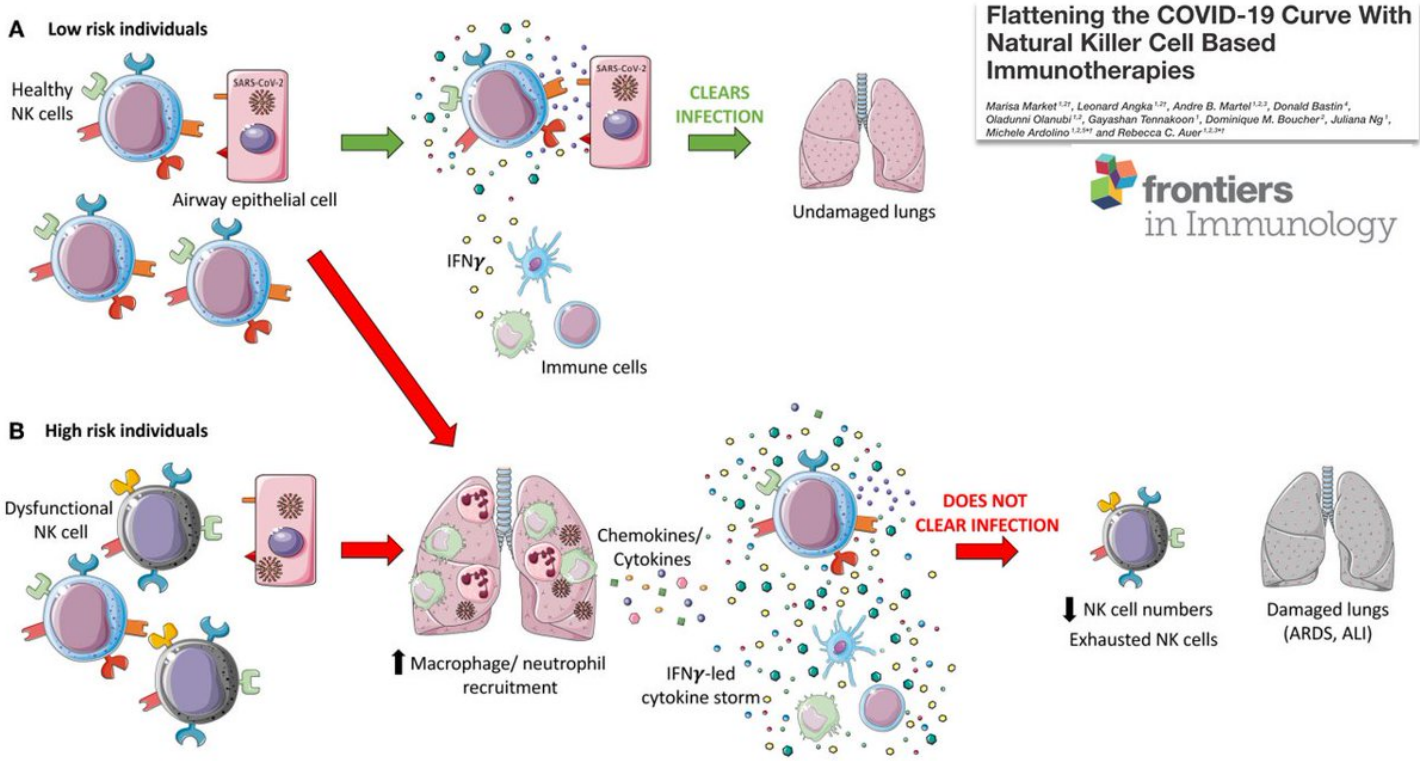


(2/n)
- The NK cell proliferation ability declines with age: older people have a decreased ability to produce NC cells rapidly: https://t.co/VZ9PSW5OBU



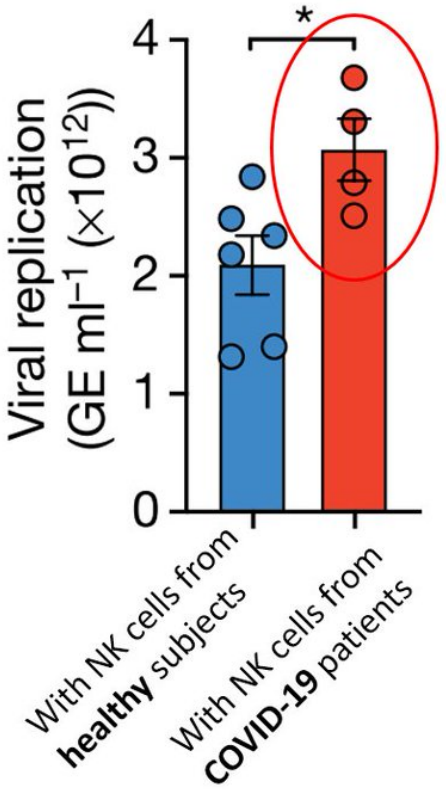
(3/n)

- As early as June 2020, it was hypothesised that NCCs could be key in explaining severe COVID-19 courses: https://t.co/yJPXeXcku0



(4/n)

- Indeed, it was later found that NK cells from COVID-19 patients do not function well:https://t.co/aEK9KpaA45



NK cells isolated from patients admitted to hospital with COVID-19 were significantly less effective in reducing the viral load compared with NK cells from healthy donors

nature

Untimely TGFβ responses in COVID-19 limit antiviral functions of NK cells

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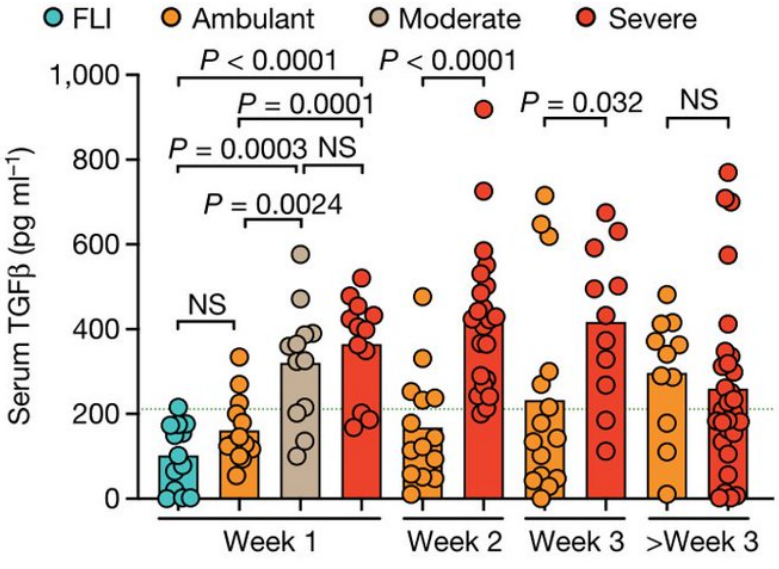
(5/n)

- The activity of NK cells is downregulated by the cytokine transforming growth factor-β (TGFβ)
- Blood serum of patients with severe COVID-19 inhibits NK cell function in a TGFβ-dependent manner: https://t.co/aEK9KpaA45



Serum of patients with severe COVID-19 inhibits NK cell function in a TGFβ-dependent manner.
Serum levels of active TGFβ. Independent measurements (mean) from 13 patients with FLI (n = 13) and 66 patients with COVID-19 (30 severe, n = 74; 7 moderate, n = 12; 39 ambulant, n = 53) at indicated time points after symptom onset (group >3 weeks contains samples from weeks 4 and 5). The dashed line indicates the median TGFβ serum level of 34 healthy donors. Patients receiving corticosteroids were excluded.

Untimely TGFβ responses in COVID-19 limit antiviral functions of NK cells

Mario Witkowski, Caroline Tizian, ... Andreas Diefenbach + Show authors

Nature **600**, 295–301 (2021)

(6/n)

- An untimely early production of TGFβ and associated NK cell dysfunction is a hallmark of severe COVID-19

- The inhibition of untimely TGFβ production & the promotion of NK cell function may positively affect SARS-CoV-2 control on multiple levels: https://t.co/zjeCnASWhx

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International Journal of Biological Sciences

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Editorial

A potential treatment of COVID-19 with TGF-β blockade

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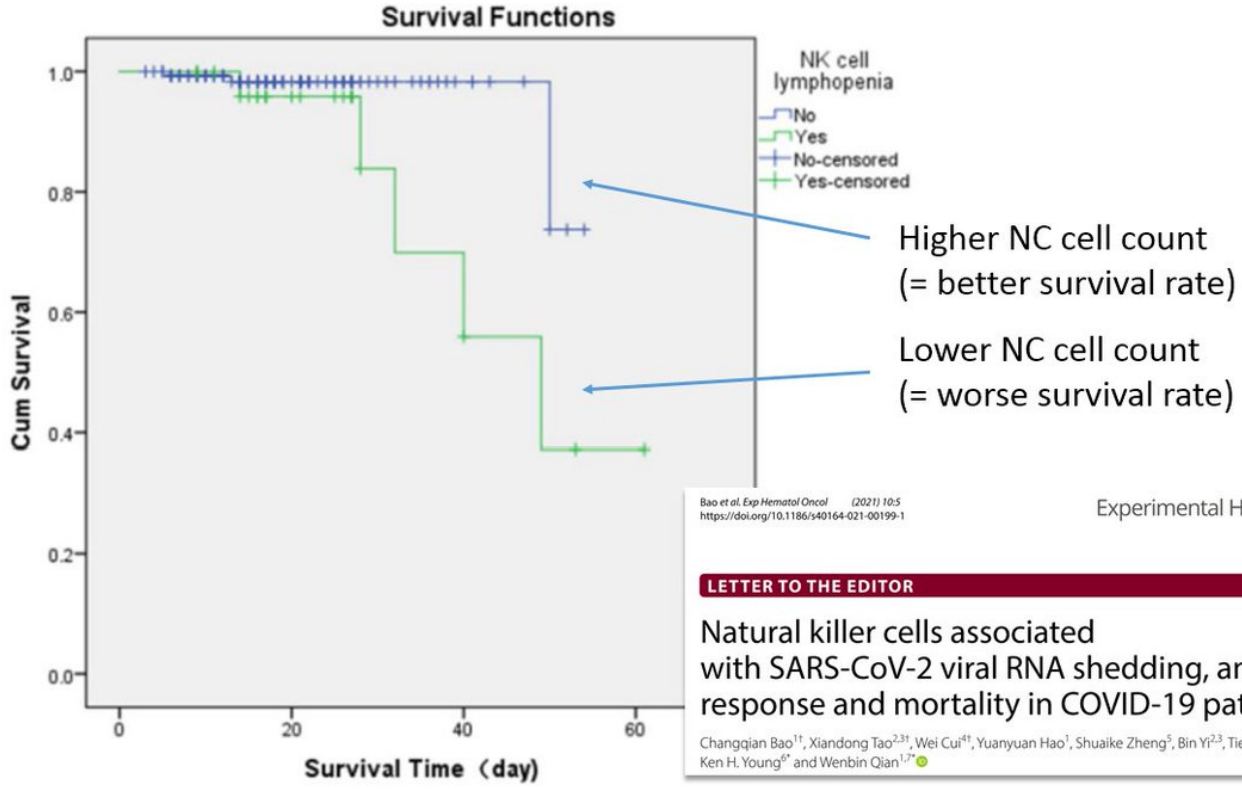
«Based on the clinical and laboratory features and lung pathological manifestations of COVID-19 patients combined with published pathological and immunological features present in the lungs of previous SARS patients, I hereby propose a potential immunotherapy for the severe COVID-19 through blockade of transforming growth factor-beta (TGF-β).»

(7/n)

- A lower NK cell count in COVID-19 patients has been shown to be correlated with a lower survival rate:https://t.co/EUQkL76GhW



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https://doi.org/10.1186/s40164-021-00199-1

Experimental Hematology & Oncology

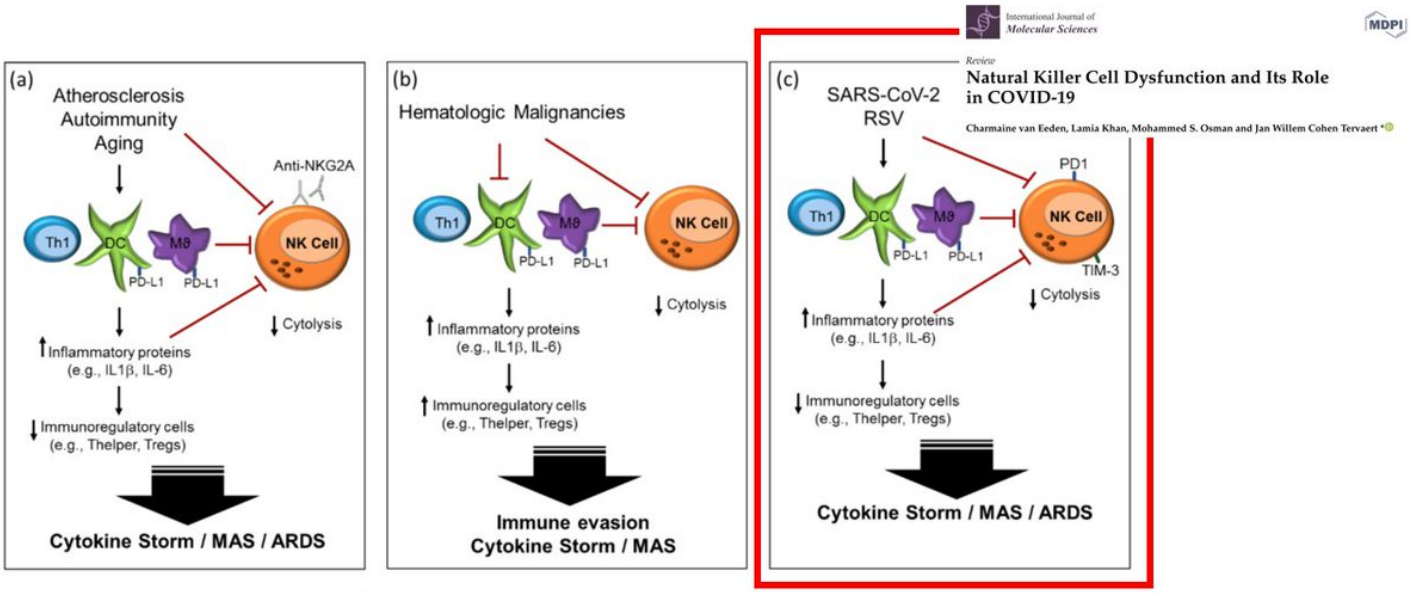
LETTER TO THE EDITOR Open Access

Natural killer cells associated with SARS-CoV-2 viral RNA shedding, antibody response and mortality in COVID-19 patients

Changqian Bao[1†], Xiandong Tao[2,3†], Wei Cui[4†], Yuanyuan Hao[1], Shuaike Zheng[5], Bin Yi[2,3], Tiewen Pan[2], Ken H. Young[6*] and Wenbin Qian[1,7*]

(8/n)

- NK cell dysregulation as a key factor in COVID-19 was also highlighted 1.5 years ago: https://t.co/Dg0KmYT2iS
- “Restoration of NK cell effector functions has the potential to correct the delicate immune balance required to effectively overcome SARS-CoV-2 infection.”



International Journal of Molecular Sciences
MDPI
Review

Natural Killer Cell Dysfunction and Its Role in COVID-19

Charmaine van Eeden, Lamia Khan, Mohammed S. Osman and Jan Willem Cohen Tervaert *

Figure 2. Natural killer cell dysregulation in (**a**) systemic diseases; (**b**) hematologic malignancies; (**c**) SARS-CoV-2. (**a**) Immune imbalance in atherosclerosis, autoimmunity and ageing leads to excess inflammation; (**b**) Hematologic malignancies trigger both excess inflammation and immune invasion; (**c**) SARS-CoV-2 and respiratory syncytial virus (RSV) trigger immune imbalances which result in a disproportionate inflammatory response.

(9/n)

- Vitamin D (our old friend!) also plays a role for the NK cells. Vitamin D deficiency correlates with a reduced number of NK cells in COVID-19 patients: https://t.co/YNrvKIrlgj

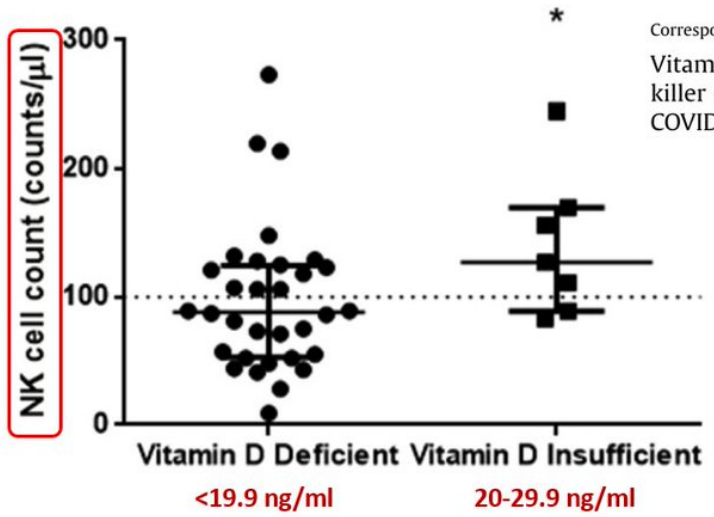


Figure 1. Vitamin D deficiency and NK cell count. Vitamin D levels were measured in 39 COVID-19 patients on hospital admission (within 48 h). We subsequently divided our cohort into two groups based on their vitamin D levels; vitamin D deficient (≤19.9 ng/ml, N = 32) and vitamin D insufficient (20-29.9 ng/ml, N = 7). Non-parametric Mann-Whitney revealed a statistically significant relationship between the count of NK cells in vitamin D deficient and insufficient patients. Data are represented as scatter plots. Line in the middle, median value; lower and upper lines, 25th to 75th centiles; horizontal line, threshold for NK lymphopenia. *p <0.05. NK= Natural killer.

Correspondence

Vitamin D deficiency correlates with a reduced number of natural killer cells in intensive care unit (ICU) and non-ICU patients with COVID-19 pneumonia

Hellenic Journal of Cardiology 62 (2021) 381–383

Hellenic Journal of Cardiology

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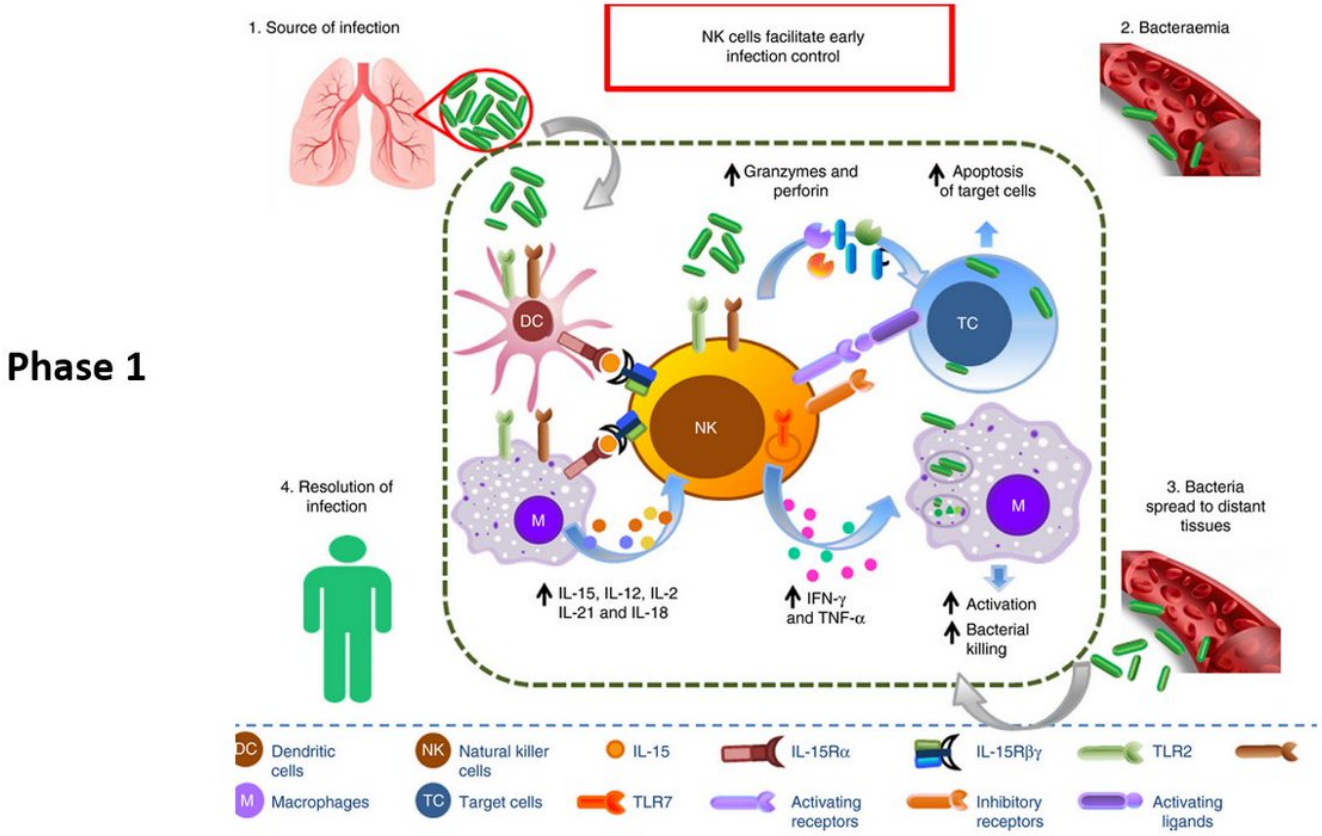
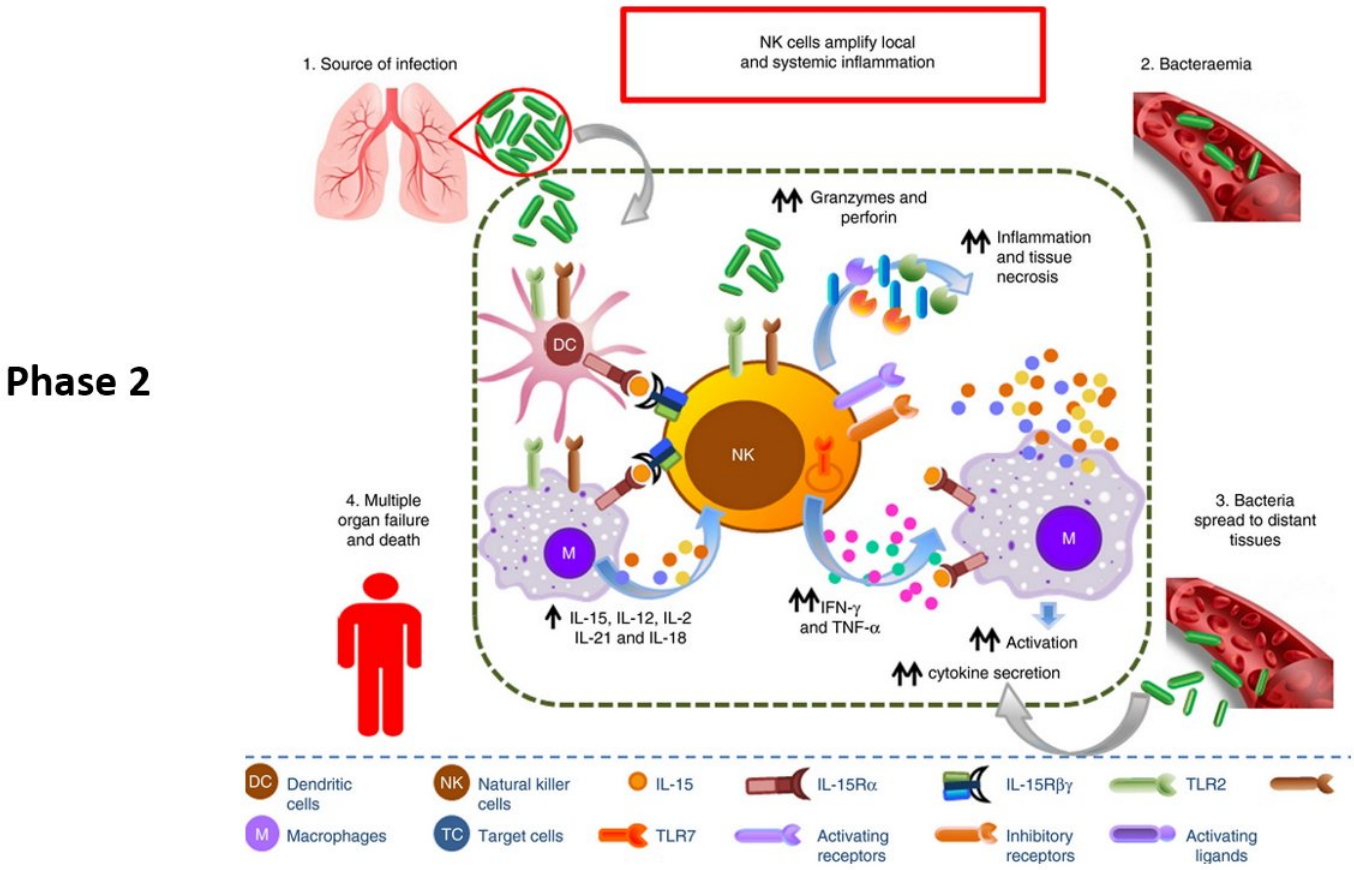
(10/n)

- While early NK cell stimulation & IFN-γ production is bene■cial to combat infections, excessive & prolonged stimulation of NK cells leads to reduced NK cell numbers & an exhausted phenotype associated with increased systemic in■ammation: https://t.co/vPpfKbntne



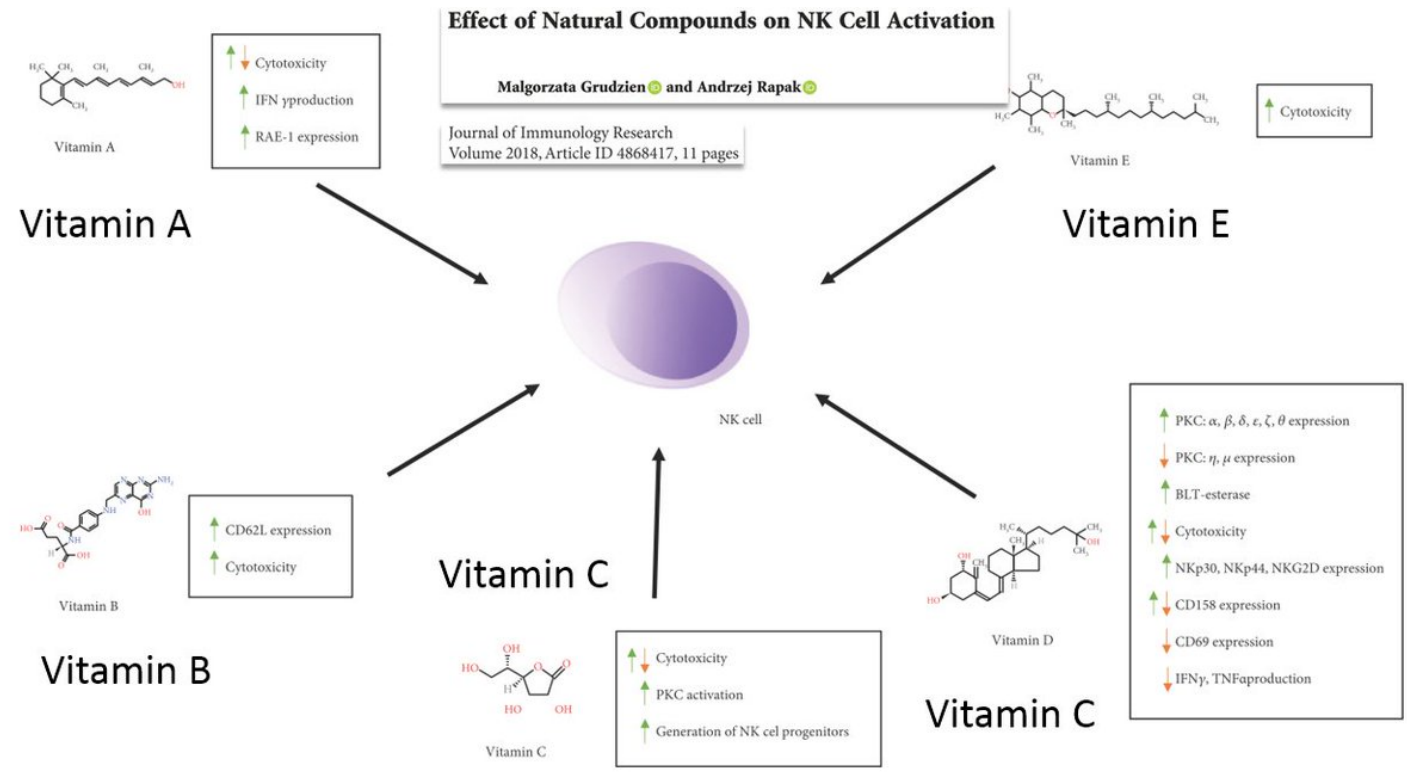
(11/n) Phase 1 ■ Phase 2



(12/n)

- The vitamins A, B, C, D and E influence NK cell activity:

https://t.co/37ucftVsXp



(13/n) Also phytochemicals haven an effect on NK cell activity:

https://t.co/37ucftVsXp

Table 1: The effect of natural compounds on NK cells.

Substance name	Effect on NK cells	References
Genistein	Increased/decreased cytotoxicity	[56–60]
Curcumin	Increased NO production, increased cytotoxicity	[61–67]
Ginseng extract	Increased cytotoxicity and granzyme B expression	[68–71]
Garlic extract	Increased cytotoxicity and cell number	[72–74]
Resveratrol	Increased cytotoxicity, JNK, ERK1/2 MAP kinase activity, perforin and NKG2D expression, and IFN-γ production	[75–78]
Ashwagandha extract	Increased cell number and CD69 expression	[79–83]
Ingenol mebutate	PKC activation, impaired cytotoxicity, and degranulation	[84–87]
Kumquat pericarp extract	Increased cytotoxicity and IFN-γ production	[88–90]
Prostratin	PKC activation, increased NKG2D expression and antiviral activity, impaired degranulation, and cytokine production	[87, 91]
Lectins	Increased cytotoxicity	[92]
Polysaccharides	Increased cytotoxicity and proliferation	[93–95]

Effect of Natural Compounds on NK Cell Activation

Malgorzata Grudzien and Andrzej Rapak

Journal of Immunology Research
Volume 2018, Article ID 4868417, 11 pages

(14/n) To summarize:

- NK cells play an important role in COVID-19 disease severity and outcomes
- Age, vitamin deficiencies, etc. negatively affect the functioning of NK cells
- Therapeutic approaches for COVID-19 should include support of NK cell function