

## 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



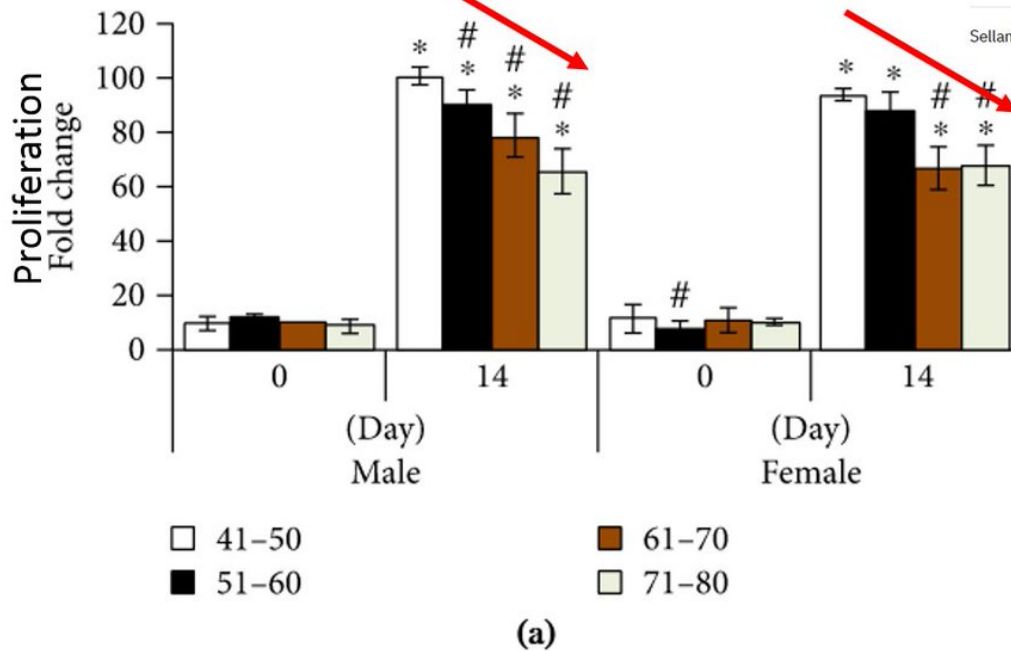
**Natural killer cell**

**Red blood cell**

(2/n)

- The NK cell proliferation ability declines with age: older people have a decreased ability to produce NK cells rapidly:

<https://t.co/VZ9PSW5OBU>

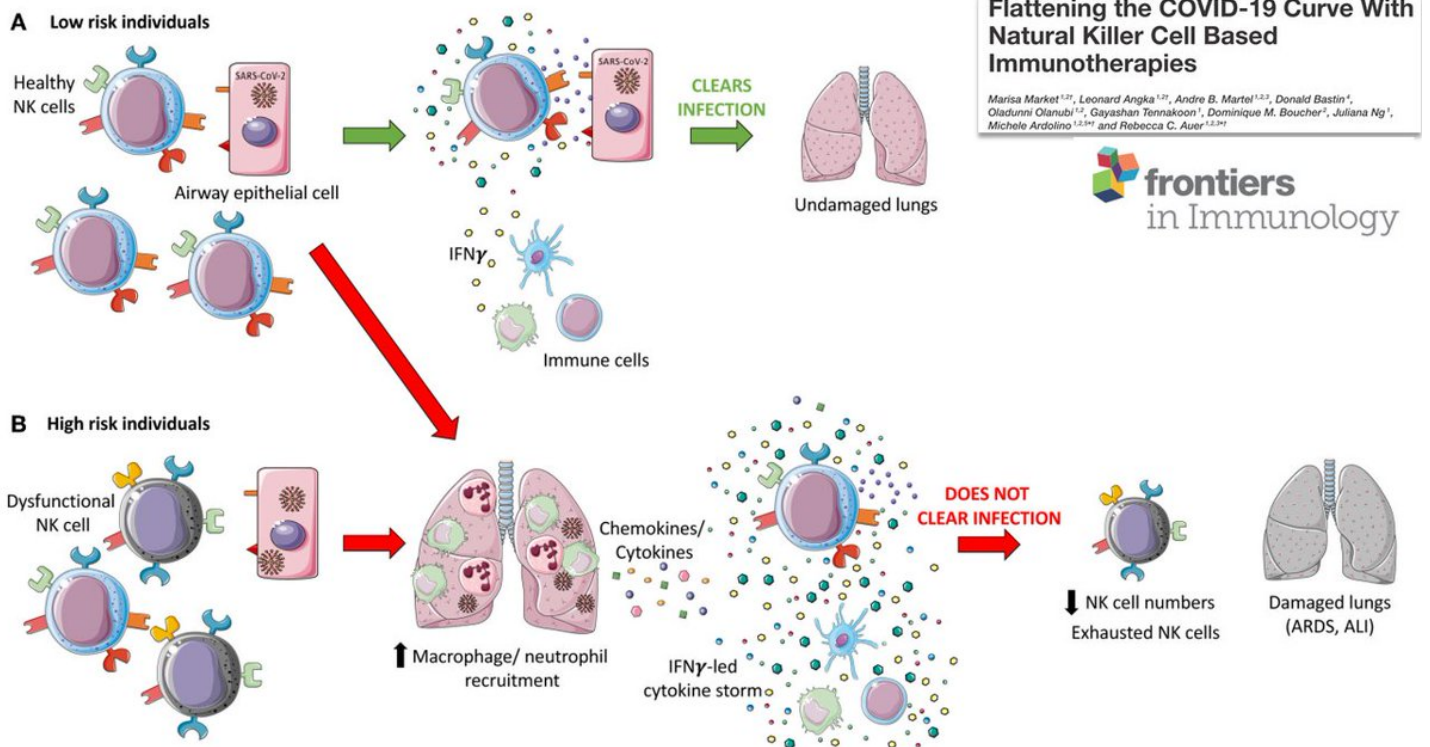
Sellamuthu Subbanna Gounder,<sup>1</sup> Basri Johan Jeet Abdullah,<sup>2</sup>

**NK cells from all age groups were dramatically divided and manufactured to almost more than 90% purity.** Cell fold was significantly increased at all age groups in both genders after 14 days of culture. In comparison with aging, NK cell growth in elderly people was significantly lower than that in younger people.

(3/n)

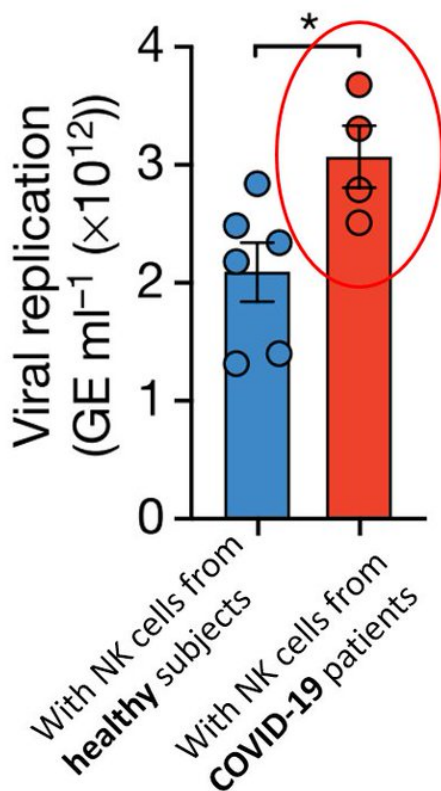
- As early as June 2020, it was hypothesised that NCCs could be key in explaining severe COVID-19 courses:

<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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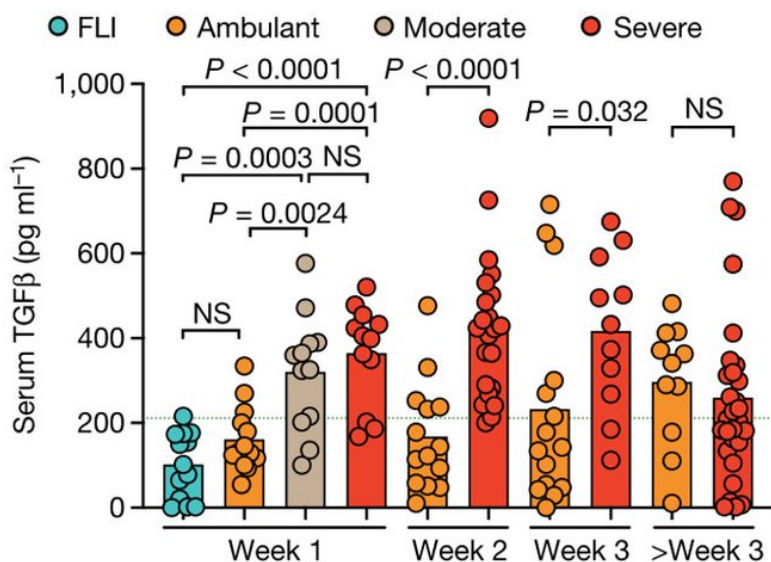
Check for updates

Mario Witkowski<sup>1,2,3,31,32</sup>, Caroline Tizian<sup>1,2,31</sup>, Marta Ferreira-Gomes<sup>4,31</sup>, Daniela Niemeyer<sup>5,6</sup>, Terry C. Jones<sup>3,6,7</sup>, Frederik Heinrich<sup>4</sup>, Stefan Frischbutter<sup>8,9</sup>, Stefan Angermair<sup>10</sup>, Thordis Hohnstein<sup>12</sup>, Irene Mattioli<sup>12</sup>, Philipp Nawrath<sup>12</sup>, Sophie McEwen<sup>12</sup>, Silvia Zocche<sup>11</sup>, Edoardo Viviano<sup>12</sup>, Gitta Anne Heinz<sup>4</sup>, Marcus Maurer<sup>8,9</sup>, Uwe Kölsch<sup>13</sup>, Robert Lorenz Chua<sup>14</sup>, Tom Aschman<sup>15</sup>, Christian Meisel<sup>13,16</sup>, Josefine Radke<sup>15</sup>, Birgit Sawitzki<sup>16</sup>, Jobst Roehmel<sup>17</sup>, Kristina Allers<sup>18</sup>, Verena Moos<sup>18</sup>, Thomas Schneider<sup>18</sup>, Leif Hanitsch<sup>16</sup>, Marcus A. Mall<sup>17,19</sup>, Christian Conrad<sup>14</sup>, Helena Radbruch<sup>15</sup>, Claudia U. Duerr<sup>20</sup>, Joseph A. Trapani<sup>21</sup>, Emanuela Marcenaro<sup>22</sup>, Tilmann Kallinich<sup>12,23</sup>, Victor M. Corman<sup>24</sup>, Florian Kurth<sup>24,25</sup>, Leif Erik Sander<sup>26,27,28</sup>, Christian Drost<sup>26</sup>, Sascha Treskatsch<sup>10</sup>, Pawel Durek<sup>4</sup>, Andrey Kruglov<sup>26,27,28</sup>, Andreas Radbruch<sup>29</sup>, Mir-Farzin Mashreghi<sup>4,30,32</sup> & Andreas Diefenbach<sup>1,2,3,32</sup> ✉

(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 TGF $\beta$  production & the promotion of NK cell function may positively affect SARS-CoV-2 control on multiple levels: <https://t.co/zjeCnASWhx>

Editorial

## A potential treatment of COVID-19 with TGF- $\beta$ blockade

WanJun Chen 

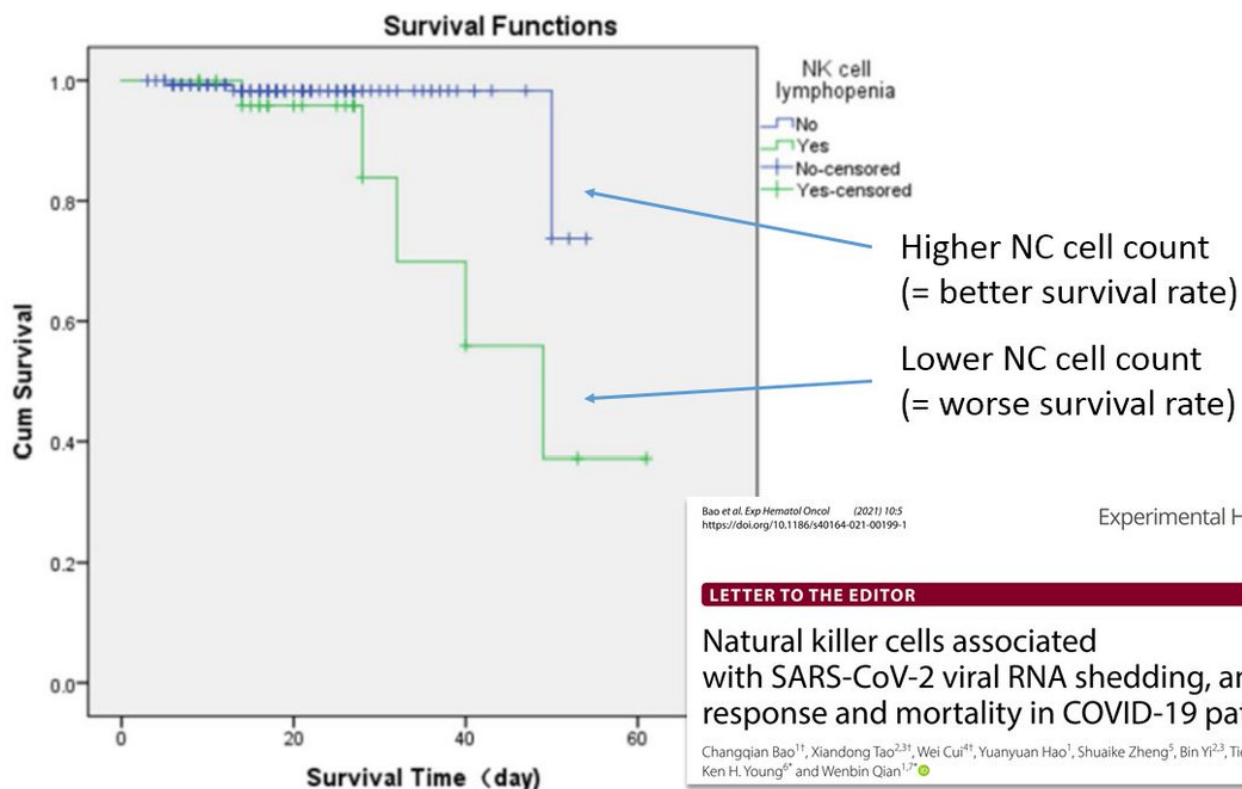
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«Based on the clinical and laboratory features and lung pathological manifestations of COVID-19 patients combined with published pathological and immunological features present in the lungs of previous SARS patients, I hereby propose a potential immunotherapy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

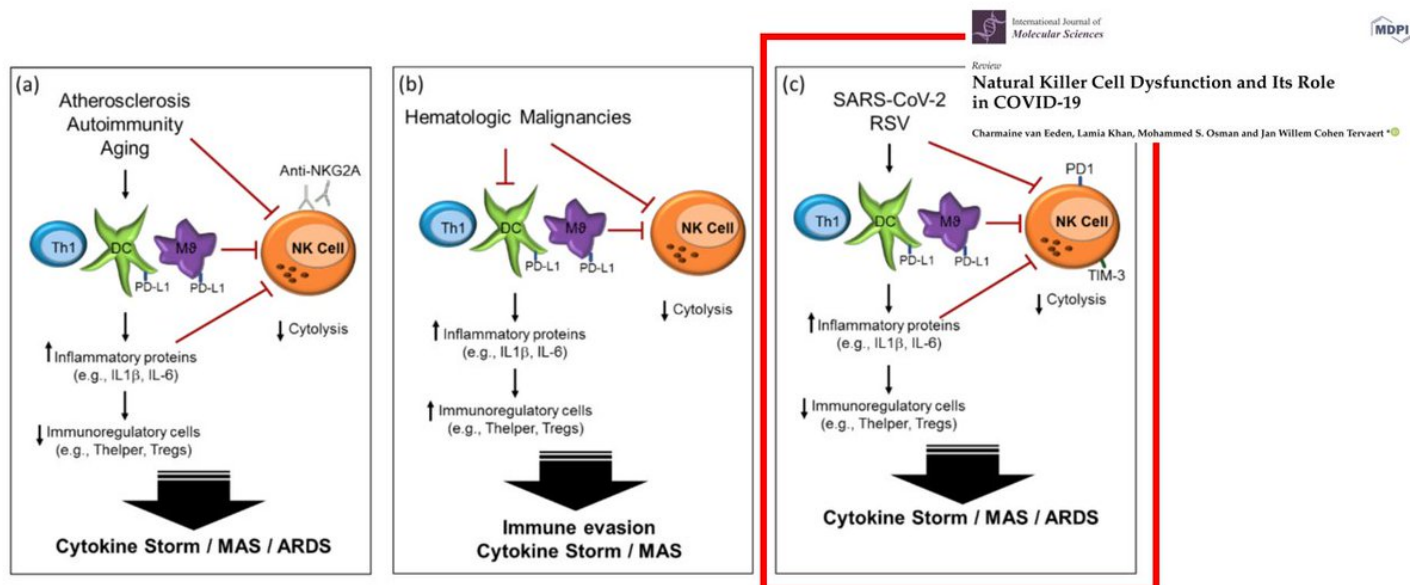
(7/n)

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



(8/n)

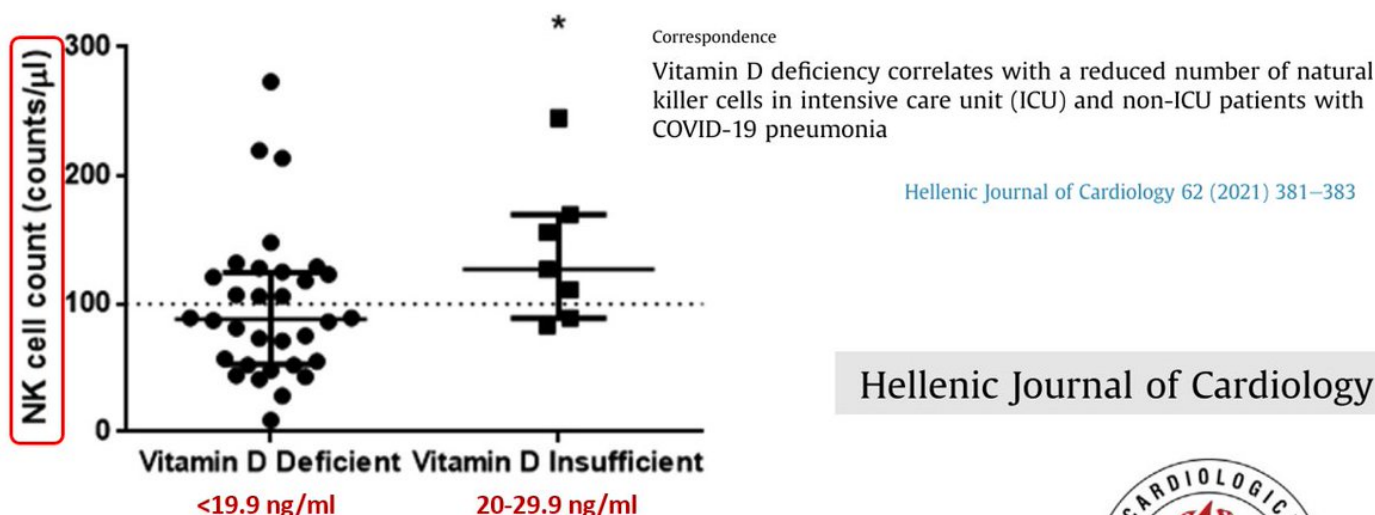
- NK cell dysregulation as a key factor in COVID-19 was also highlighted 1.5 years ago: <https://t.co/Dg0KmYT2iS>
- “Restoration of NK cell effector functions has the potential to correct the delicate immune balance required to effectively overcome SARS-CoV-2 infection.”



**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/YNrvKlrlgI>



**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 ( $\leq 19.9$  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, 25<sup>th</sup> to 75<sup>th</sup> centiles; horizontal line, threshold for NK lymphopenia. \* $p < 0.05$ . NK= Natural killer.

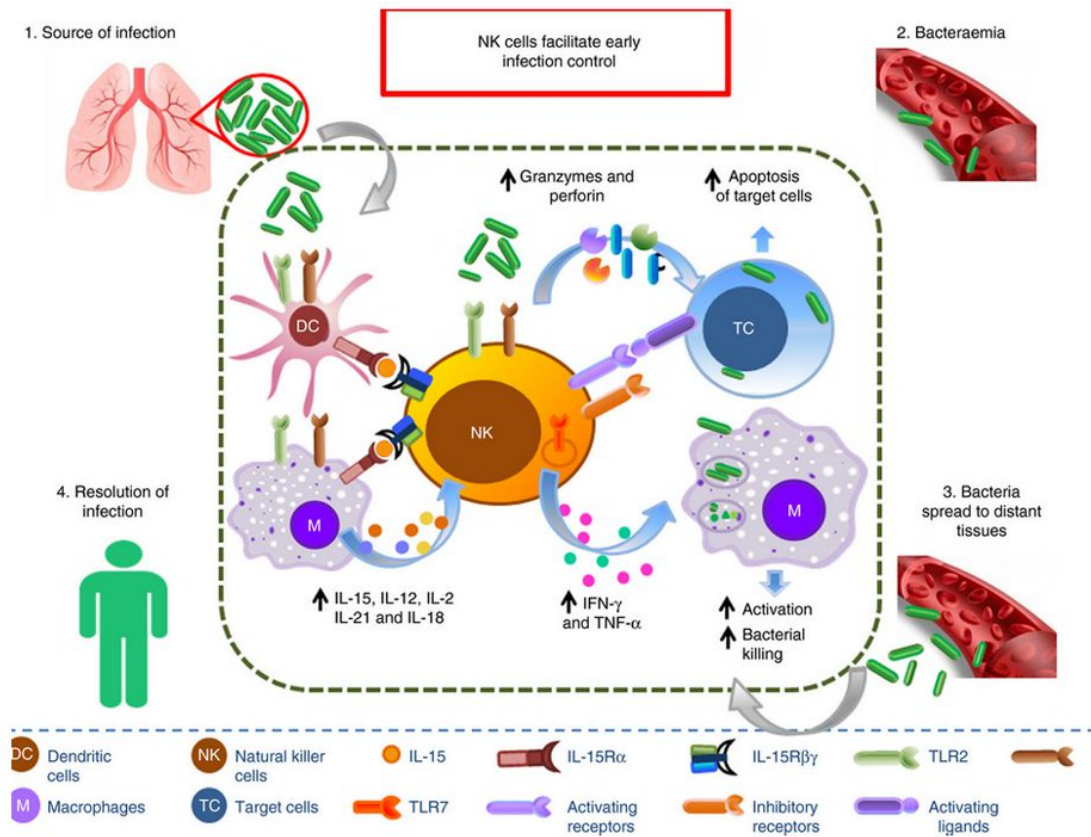


(10/n)

- While early NK cell stimulation & IFN- $\gamma$  production is beneficial to combat infections, excessive & prolonged stimulation of NK cells leads to reduced NK cell numbers & an exhausted phenotype associated with increased systemic inflammation:

<https://t.co/vPpfKbntne>

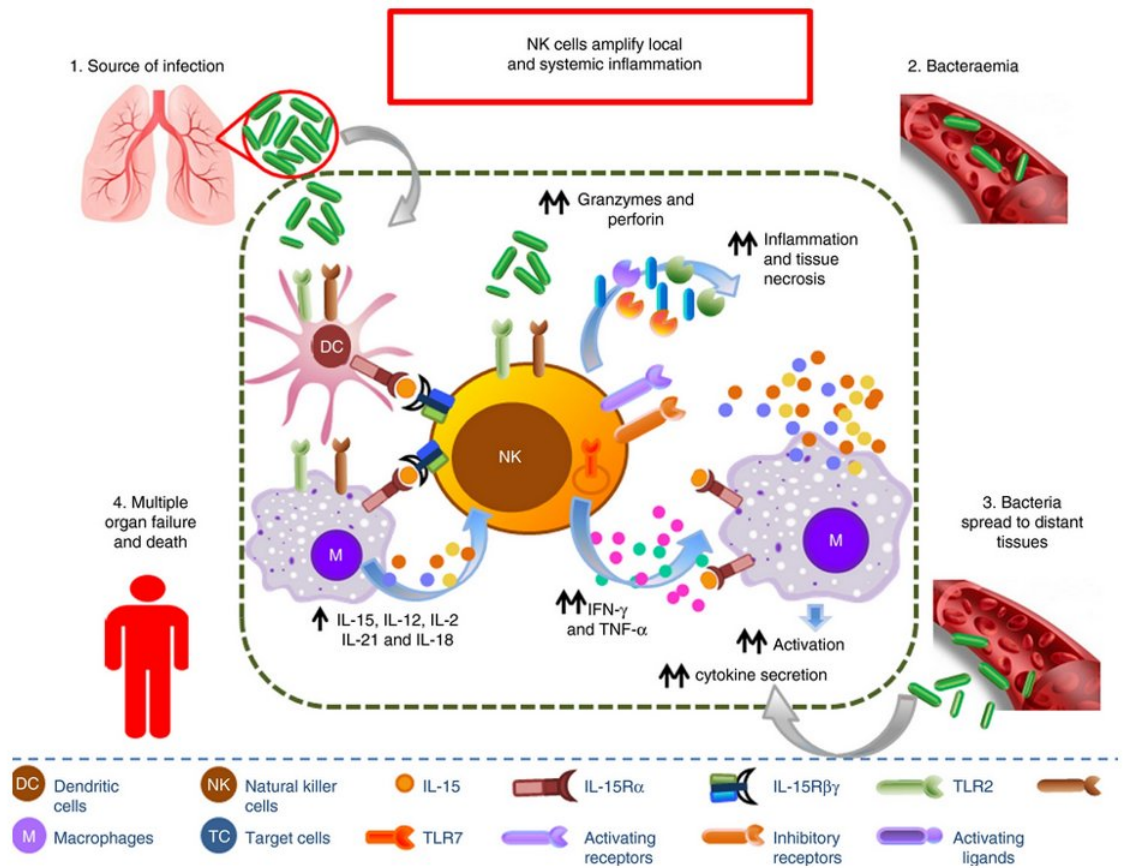
## Phase 1



(11/n) Phase 1 ■ Phase 2



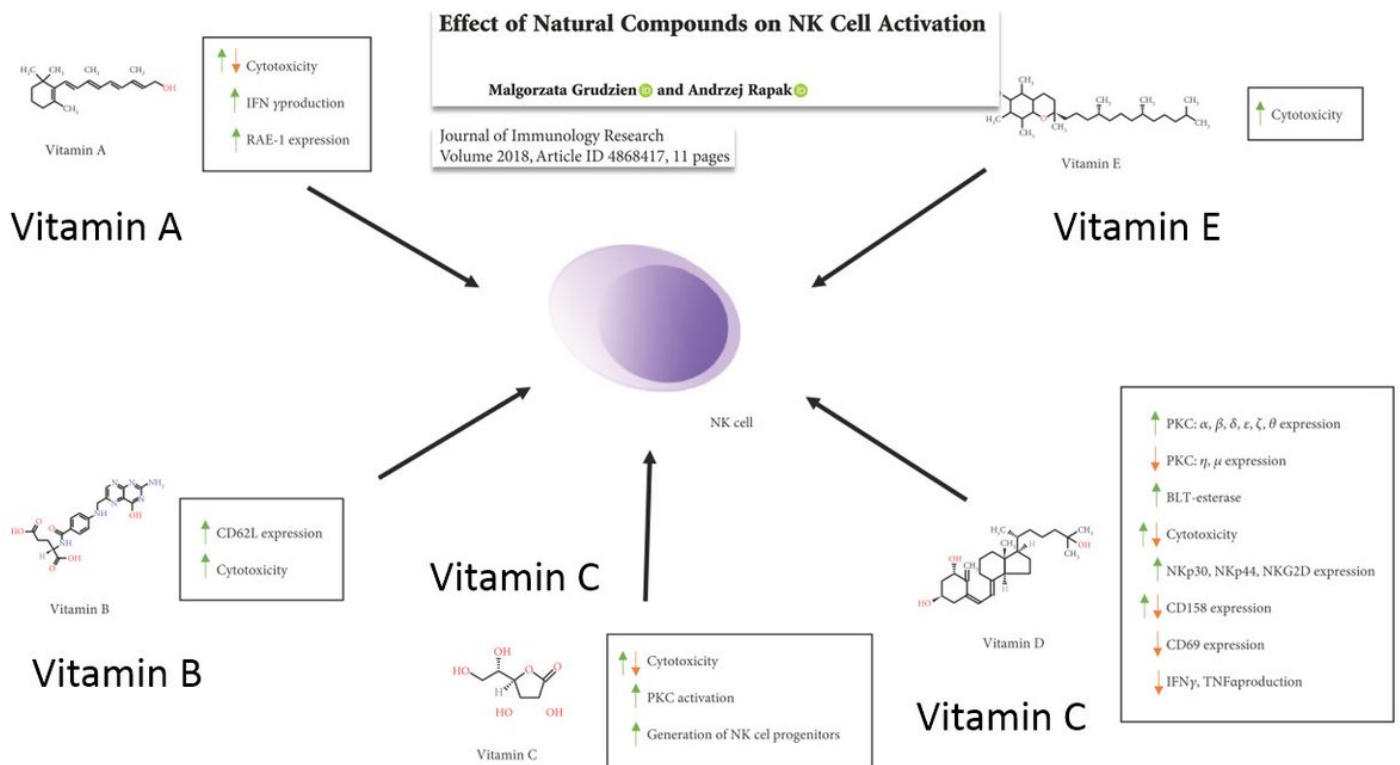
## Phase 2



(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- $\gamma$ 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- $\gamma$ 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