UNDERSTANDING THE THYMUS WITH APPLICATIONS TO COVID-19 PATHOPHYSIOLOGY AND SUSCEPTIBILITY WITH POTENTIAL THERAPEUTICS

A PREPRINT

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ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus continues to severely impact health and economies around the world. However, the underlying mechanisms behind the disease are still under investigation. Of particular interest to the scientific community is the reason why children are less prone to severe COVID-19 disease. The mild clinical course in the pediatric population suggests that the virus may not be the problem and instead that the problem may be one of host susceptibility. A review of the literature on SARS-CoV-2 and diversity of the immune system produced the hypothesis that thymic output and therefore a lack of diversity of T-cell receptor (TCR) affinity is causally linked to SARS-CoV-2 susceptibility. Statistical analysis of epidemiological data from Canadian COVID-19 infections is provided in support of this theory. Furthermore, the lymphopenia (low abundance of lymphocytes in the blood) observed in severe clinical cases of SARS-COV-2 can be explained by a delay in activation of the adaptive immune system, due in part to the rarity of SARS-CoV-2 specific clonotypes being maintained in the lymph nodes and blood. Non-specific (with respect to TCR) chemokine signalling in the absence of clonal expansion of T-cells would present as lymphopenia in a respiratory infection. We note that there are existing agents, such as thymosine-α-1-Fc (TA-1) that have been shown to augment the bioavailability of naive CD8 and CD4 cells, having undergone V-D-J-recombination. This would help the host by stimulating the production of additional diversity of T-cell receptor affinity to facilitate the production of T-cell clonotypes specific to SARS-CoV-2 epitopes as well as priming dendritic cells by increasing the expression of co-stimulatory molecules. Furthermore, the lack of type 1 interferon response suggests that a combination of TA-1 and $\alpha\beta$-interferon may provide the synergistic effects necessary to effectively engage to adaptive immune system in a timely manner, where deemed appropriate by the treating physician.

1 Introduction

The adaptive immune system has evolved over the course of millions of years to manage infections by a wide range of microorganisms including the most current and imminent threat SARS-CoV-2. SARS-CoV-2 is thought to have originated from a zoonotic transmission [6] and previous research had identified a SARS-like virus as a potential threat in Chinese bat population in 2015[36]. A notable clinical manifestation of a severe case of COVID-19 is lymphopenia, associated with poor outcomes[53]. Understanding the cause of lymphopenia (a low abundance of lymphocytes in the blood) is crucial to understanding SARS-CoV-2 pathogenesis and to developing a successful treatment.

A key element of mounting an effective adaptive response involves maintaining an adequately diverse and numerous pool of T-cells capable of responding to novel antigens[40]. The generation and selection of naive T-cells is an extremely efficient system that has evolved to provide a balanced reaction which minimizes harm to the host[42]. The diversity of the clonotypes with respect to TCR composition being maintained is an important measure of the host's ability to respond to antigenic challenges[41]. The number of bioavailable cells capable of responding to a specific antigenic challenge influences the magnitude of the immune response. This crucial element of the host response to viral infections involves the creation of a pool of memory T-cells, capable of quickly responding in large numbers with repeat exposures. We propose that a plausible explanation for the age-specific susceptibility to novel antigenic fitness challenges is a decrease in diversity of receptor affinity, maintained in part by the thymus, which decreases exponentially with age in terms of both size and output[44]. More specifically, it is the number of available T-cells and their diversity which together help ensure a successful host-defense. The fact that children appear to have a milder clinical course of COVID-19 [23] suggests that the problem is not the virus but rather one of the aging host. This is supported by the low type 1 interferon response measured in SARS-CoV-2 infected cells [60] which should be interpreted as a lack of early deleterious effects.

In addition to age-related involution and associated decreased function of the thymus, the hormones which regulate mammalian thymic output become imbalanced in certain pathological conditions like metabolic syndrome or obesity [63, 46]. This hormonal imbalance affects the thymic output and results in a less diverse bioavailable T-cell repertoire. This makes an individual more susceptible to novel antigenic challenges like certain cancers[14] and perhaps SARS-CoV-2. In fact Obesity and metabolic syndrome have both been shown to be associated with poor outcomes in covid-19 disease [28, 65]. In a very novel viral infection where the virus-specific clonotypes had not been maintained in large quantities, a lack of diversity would delay the presentation of peptides by dendritic cells (DCs) to a sufficient number of virus-specific T-cells. Cellular immunity has been shown to be efficient in [18] SARS-CoV-2 infection as a result of the lack of seroconversion in certain familial COVID-19 cases. We review the potential role of the thymus as a causal factor in inducing susceptibility to COVID-19. An plausible explanation for the lymphopenia observed in severe clinical cases of SARS-CoV-2 is provided and furthermore, we suggest that Thymosin-alpha-1-Fc, with the possible addition of type I Interferon, be considered to help initiate the adaptive response by increasing the number of T-cells with naive diversity made available in the blood through thymic output. Recent clinical data, made available subsequent to the development of this hypothesis, showed that TA-1 had been efficient at reducing mortality[30]. We suggest that this treatment may be a result of a more efficient initial engagement of virus-specific clonotypes by engaging the highly efficient innate arm of the immune system evolved to respond to viral challenges in a balanced way.

2 Review

2.1 Thymus and T-cell generation

The thymus is a key component of the immune system, specifically in terms of the development of cellular immunity [38]. The thymus is primarily responsible for producing naive T-cells with a diverse range of functions and TCR compositions[57]. This stream of constant diversity of naive T-cells is important in responding to molecular patterns that the immune system has never encountered before as these cells would not have undergone clonal expansion in the absence of activation. A feature of this adapted cellular defence mechanism is the creation of an abundance of memory T-cells in response to a successful adaptive response to a viral antigenic challenge. These memory cells are capable of quickly responding to recurrent antigenic challenges of a similar nature in terms of the molecular patterns of the proteins to be identified. The diversity in the naive T-cell population is generated through V-D-J and V-J recombination in the thymus which allows thymocytes to generate T-cell receptor (TCR) diversity through alternative splicing [20, 10]. The thymus is organ within which diversity can be safely developed without risking frequent auto-immune reactions since thymocytes expressing TCRs that bind to tissue-specific antigens are removed[24].

This diversity of affinity is achieved by a tightly regulated selection process in the thymus, facilitated in part by the binding of T-cell receptors to major histo-compatibility complex (MHC) sites and Autoimmune Regulator (AIRE) genes which make available tissue-specific self-antigens to developing thymocytes [7]. T-Cells that recognize certain host-specific tissues are, for the most part, removed [61]. Most thymic naive T-cells have undergone V-D-J recombination [59] which generates a random *random* distribution of TCRs not yet subject to selection/deletion due to competition within the lymph nodes. It is important to understand that there is a qualitative difference in the patterns maintained in the lymph nodes and the ones generated by this process. The Recombination activating gene (RAG), necessary for this recombination, leads to immune disorders when deficient as the development of functional T and B cells is not possible[15]. The involution of the thymus, associated with a reduced output of naive T-cells [61] has been suggested to be a result of a hormonal mechanism regulated in part by the production of hormones such as Progesterone (PG)[58], Growth Hormone (GH), Ghrelin (GR), [55] and possibly estrogen [33].

The reduction in thymic output is progressive throughout life but exponential in nature, accelerating after 60 years of age in men and again after 80 years of age in both men and women [39]. The effect of this drop in thymic output on T-cell receptor diversity in the peripheral T-cell pool is an ongoing subject of investigation [8]. A key step in assessing thymic contribution to the available T-cell pool is differentiating naive T-cells produced in the thymus from those resulting from peripheral naive T-cell replication. Recent thymic emigrants (RTEs) can be distinguished from naive T-cells produced via extra-thymic cell division by the presence of T-cell Receptor excision circles (TRECs) [4]. TRECs in the DNA of thymocytes [51] are formed when V-D-J recombination occurs in the thymus [4]. Naive T-cells produced in the periphery as a result of cell division do not undergo V-D-J recombination and therefore do not possess TRECS. Understanding the difference in diversity from these two sources of naive T-cells may be crucial to understanding the susceptibility to certain diseases. This includes SARS-CoV-2 as well as certain cancers that seem to follow an exponential distribution similar to and coinciding with the involution of thymic output[44]. RTEs were once thought not to be important after adolescence as a result of extra-thymic maintenance of the naive T-cell pool [8], however, studies have shown that RTEs continue to contribute to the diversity of the peripheral T-cell repertoire throughout the course of life in terms of receptor distribution and function [24, 57]. Furthermore, the development of methods to distinguish recently produced thymic TREC T-cells from peripherally maintained TREC cells have been created and involve measuring signal joint TRECs and coding joint TRECs and have confirmed a reduction in thymic production with age, more prominent in men than women for most decades[39]. Traditionally, there has been little appreciation of the role of age-associated thymic involution with respect to clinical pathophysiology, but more recent work is beginning to suggest a greater clinical impact[44, 34, 63].

2.1.1 T cell maturation

The maturation of T-cells occurs in lymph nodes through a selection mechanism which favours frequently activated clonotypes as a result of cell division following activation and a competition for limited survival signals from molecules like IL-7, IL-15 [29, 31] and interactions with peripheral MHC sites[9]. The combination of thymic output, lymph node maintenance, there exists balance of diversity and specificity. In aging lymph nodes, not only is there an oligoclonal population of T-cells in terms of TCR diversity but these cells have matured into specific subtypes, optimized for frequent antigenic challenges[26]. Therefore, as one ages, there is a tradeoff between diversity and specificity which favors diversity in the young and specificity in the aging population.

2.1.2 Maintenance of diversity

After reaching adulthood the thymus is not thought to contribute T-cells to the lymph node population[16]. However, according to some mathematical models, the daily thymic output of a healthy adult is $10^7 - 10^8$ T cells per day and roughly equal to the number of β-clonotypes in the lymph nodes[45] estimated at approximately 10^8. Our immune system has evolved under selection pressure and therefore one would expect an optimal balance near sexual maturity. This balance is seemingly tested in zoonotic viruses which pose a significant risk to both the young and the elderly such as

2.2 SARS-CoV-2

The SARS-CoV-2 virus, having originated from an animal reservoir, would have undergone many years of selection pressure, rendering the virus less damaging to the host reservoir. Low levels of type I interferon suggest that the virus is not triggering cellular signalling to alert the the body's immune system to a viral threat [56]. However, when the virus encounters an immune system in which it has not evolved, the initiation of immune recognition pathways and subsequent inflammation produce pathogenic dynamics and the manifestation of disease. These zoonotic transmissions often lead to disease in both the young and the elderly as the young lack any memory immunity and the elderly have a senescent immune system.

2.2.1 Lymphopenia in severe COVID-19

Lymphopenia is perhaps the most important and information-carrying manifestation of severe COVID-19[54]. It suggests that there may be a movement of T-cells from the blood to the lung parenchyma that is greater than the compensation provided by a clonal expansion of T-cells in the lymph node. The insufficiency of clonal expansion may be a result of a delay in presentation of viral epitopes by dendritic cells (DCs) to virus-specific clonotypes, resulting in an increase in the amount of virus escaping initial containment. This leads to more tissue damage, which increases the non-specific recruitment of existing lymphocytes. In this situation, the hyperinflammatory state may be a result of the lack of activation rather than the overactivation of the immune response response but also the result of a lack of sufficient initial response leading to widespread damage which in turn activates the antigen-nonspecific innate immune response that leads to further tissue damage in a forward feedback loop. It is perhaps an odd fact that it is well accepted

that this disease is a result of hyperinflammation in the presence of lymphopenia. One would think that the lymphopenia suggests that the inflammatory response is inadequate for the specific affect.

3 Thymic modulation as a therapeutic target

Recent studies have shown that the thymus is a potent target for therapeutic action against a wide range of diseases including certain cancers[13]. This is unsurprising as the thymus can be thought of as the source of diversity in the body but, due to the diversity of function in T-cells[43], it can be seen as not only a means for detecting abnormal molecules but also a means of preserving homeostasis by generating molecules with similar affinities to ones that have not survived the competition mechanism in the lymph nodes.

3.1 Pregnancy and COVID and the thymus

If thymic output is important in terms of COVID-19 susceptibility, then one would expect the outcome in pregnancy to be worse as the thymus involutes during mammalian pregnancy [48]. It is thought that regulatory T-cells play a protective and immunosuppressive role to allow for fetal development [67] so that the fetus is not rejected [12]. Progesterone is thought to reduce thymic output and to modulate the immune system, which may explain why women do not seem to suffer from the lack of thymic output[27]. One particular study on the outcomes of COVID-19 pregnancies showed an abrupt increase in severity following parturition[11]. The authors of that study attributed this to an increase in blood volume, however the immediacy of the worsening symptoms may be a result of the withdrawal of progesterone secreting cells. Levels of progesterone are known to drop dramatically immediately after pregnancy [25] and as a result, the immunoprotection from progesterone is reduced. Notably, an ongoing clinical trial is investigating this:NCT04365127. The quantification of the reduction of thymic output during pregnancy is still unclear and the immunoprotective role of progesterone may play a role is suppressing exaggerated innate immune responses. Furthermore, on average, pregnant women are young and are followed quite closely and therefore have a higher quality of medical care, the age of the pregnant woman and the immunosuppressive role of progesterone suggest that the impact on the thymus cannot be easily measured with respect to COVID-19 susceptibility and severity as a result of these additional factors.

3.2 Difference between men and women

It is well documented that thymic involution is more prominent in men[22] than in women and this is consistent with the data showing that men have a more severe clinical course of severe COVID-19 than women. A statistical hypothesis test was done on the data in table 5 which involved a 2-sample test for equality of proportions without continuity correction yielding a p-value of $p < 2.2 \times 10^{-16}$. This is conclusive evidence that men are more susceptible to dying when hospitalized but only supports the hypothesis that thymic output is the causal reason behind disease susceptibility as no measurements of thymic output were taken at the time. The association in terms of the difference between men and women and the age susceptibility seem to follow the same exponential nature which occurs in thymic involution [44].

3.3 Genetic Analysis of T-cells

A recent study having analyzed the differences between exposed and unexposed blood donors in terms of their reactivity to SARS-CoV-2 antigens showed a lack of affinity to the spike protein in most of the unexposed donors[21]. The analysis showed over 50% had some form of reaction to the spike protein in terms of the CD4 cells this still leaves the possibility that a fair amount of people have no cross-reactivity whatsoever. Furthermore, the key to a successful antiviral defense involves the recruitment of cytotoxic CD8 cells which can recognize proteins being manufactured and degraded and then shown on Major Histocompatibility (MHC) type I sites. The small sample study showed very little cross-reactivity which can explain how the cell might escape detection in many cases. Furthermore, if cross-reactivity were the driving factor in host-susceptibility, you would not see such a clear exponential distribution favoring the young as seen in Figure 3. In other words, if SARS-CoV-2 were a test of specificity and previous exposure, which is what the study was essentially looking at, you would see a clear advantage for people in their most healthy, reproductive years. This does not seem to be the case for SARS-COV-2 and therefore this cross reactivity is not thought to be the main causal factor in providing protection against COVID-19.

3.4 TA-1

Thymosine-α-1, having been discovered in the 70's [19] and is known to empirically increase the amount of TREC-containing T-cells in the blood, subsequent to COVID-19 exposure[30]. This bioavailable population of thymus-derived naive T-cells has a greater diversity of TCRs than lymph node TCRs as a consequence of the generation process and the

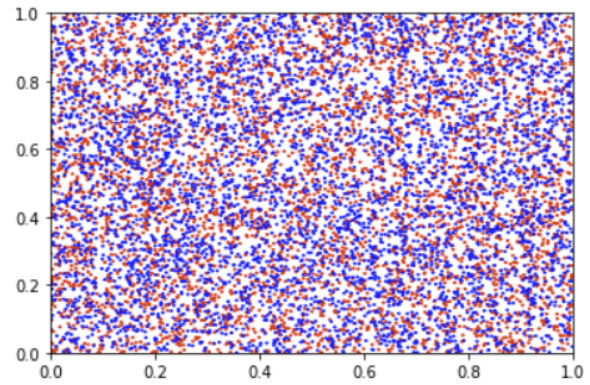

Figure 1: **Schematic of young lymph node T-cell populations**

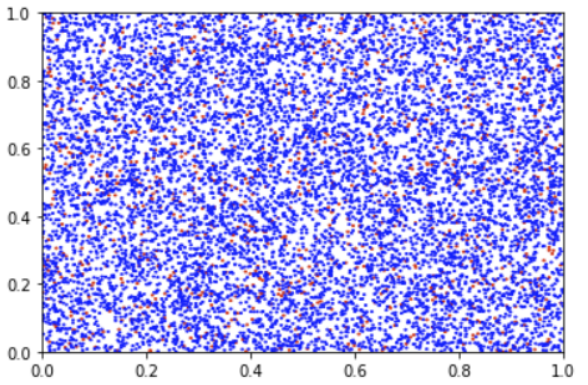

Figure 2: **Schematic of elderly lymph node T-cell populations**

fact that TCR generation is thought to only happen in the thymus. This provides a broader coverage of potential antigens and greater functional capacity. We suggest that the synergistic effect of $\alpha\beta$ interferon and TA-1 is a mechanistically plausible treatment for COVID-19 where the treatment objective is to activate the adaptive cytotoxic response in a balanced manner. Genetic studies have pointed to a low affinity of CD8 cells to the spike protein, but small sample sizes limit the possible inference[21]. The goal of this treatment is to ensure that there is a balance between the destruction by the cytotoxic lymphocytes and the immunosuppression that is eventually engaged to prevent excessive harm to the host.

Furthermore, TA-1 has shown some efficacy in the treatment of sepsis[62] where a similar relationship between low lymphocyte count and mortality has been observed[49]. The full mechanism is unclear, however TA-1 has been shown to upregulate co-stimulatory molecules CD40 and CD80 and increase the expression of Toll-like Receptors [47]. In severe COVID-19 patients, Tim-3 and PD-1 markers have been observed on T-cells which is suggestive of ineffective viral containment and cell-line exhaustion [66]. A recent review article presented results of the genetic analysic of broncheoalveolar lavage fluid (BALF) [37] from patients with different outcomes with respect to survival in SARS-CoV-2 infections. Specifically, a higher proportion of CD8+ T-cells with tissue resident signature was in the BALF of patients associated with a mild course of the disease[37]. The suggestion was that a higher proportion of infiltrating mononuclear phagocytes was associated with hyperinflammatory states and higher levels of cytotoxic IL-6. This suggests that in those who had the appropriate diversity of affinity at the location of infection - in this case the lungs, were more successful at containing the viral infection. This reinforces the notion that a timely activation of the CD8+ T-cell response is critical to host defence. The literature on TA-1 is not yet conclusive but there is enough evidence to suggest that the benefits of $\alpha\beta$-Interferon and TA-1 should be investigated in their synergistic effects in activating the adaptive arm of the immune system and activating resident immune cells, more adapted to the delicate environment of the lungs. The ultimate goal being to avoid damage-mediated recruitment which seems to be present in severe COVID-19, as evidenced by the fibrotic changes in the lungs. $\alpha\beta$-interferon is known to augment the expression of antiviral interferon stimulated genes (ISGs) which have been observed to be modestly activated by in murine SARS-CoV infections[64].

Figure 2 shows a schematic of elderly and Figure 1 a schematic pediatric populations lymph node populations. The red circles represent TREC cells whereas the BLUE cells represent cells that have undergone clonal proliferation. This example illustrates the difference in diversity between the elderly and pediatric lymph nodes and clearly illustrates how a rare red cell might be made more difficult to find in an elderly patient, a delay in presentation due to the rarity of clonotypes specific to the disease would result in the clinical manifestations consistent with severe COVID-19.

Figure 5 shows an exponential increase in probability of death with age for hospitalized patients in Canada. This exponential increase in susceptibility is consistent with an exponential decrease in thymic output[44] although direct comparison is not even attempted as a consequence of the clear multifactorial nature of disease susceptibility.

Figure 4 shows a log-linear relationship between TRECs in the blood and death by COVID-19. TREC data was obtained from a previous study that measured the TREC per millilitre of whole blood [32]. This relationship supports the conclusion but does not confirm it as measurements of TREC proportions in infected cells have not been observed. It is clear that more work must be done to more precisely measure the mechanism by which this exchange between diversity and specificity affects disease susceptibility. It should be noted that in a recent paper which studied the efficacy of TA-1, that teams of healthcare workers had been given doses of Thymosin-alpha-1 before heading to Hubei as a

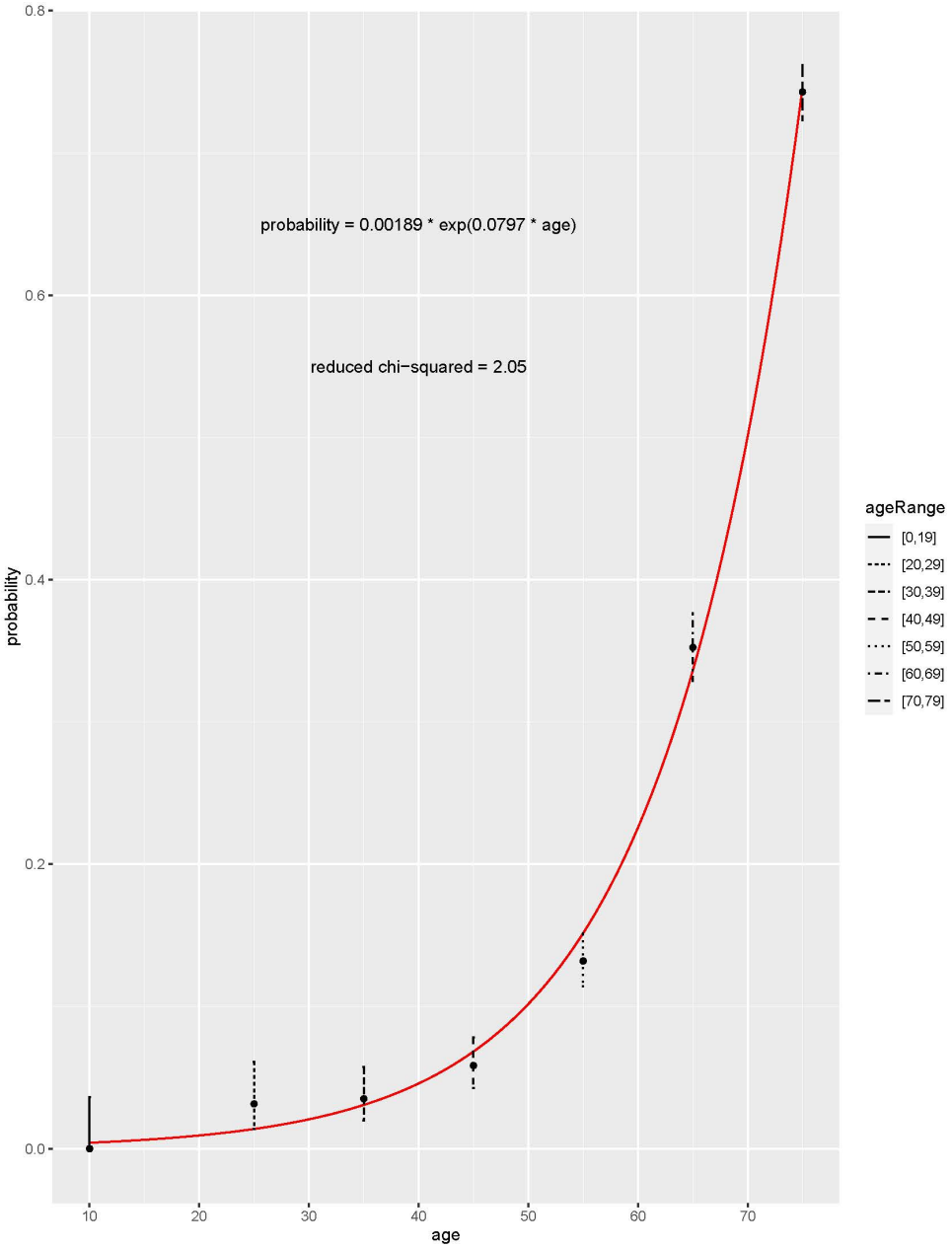

Figure 3: **Plot of the amount of deaths vs age showing a clear exponential relationship**

prophylactic measure [30]. The hypothesis of the link between thymic output and disease severity had been put forward prior to the author's knowledge of the efficacy of TA-1 in treating COVID-19 patients and therefore it is believed to be supporting evidence in favor of this hypothesis. While these hypotheses do in fact agree with all known datasets for which the author is aware, due to the pleiotropic effects of TA-1, this paper does not confirm the fact that diversity is the causal link and this must be properly investigated with the use of molecular-level high throughput techniques. The synergistic effects of TA-1 and $\alpha\beta$-Interferon intended to stimulate the adaptive response, have been previously observed in enhancing NK activity and so this approach is not completely novel[17].

3.5 Viruses as a host-defence mechanism

It is impossible to study this topic without noticing the fact that viruses seem to be an evolved means of host defence at the species level against the threat of another species monopolizing limited resources. In a situation where there are

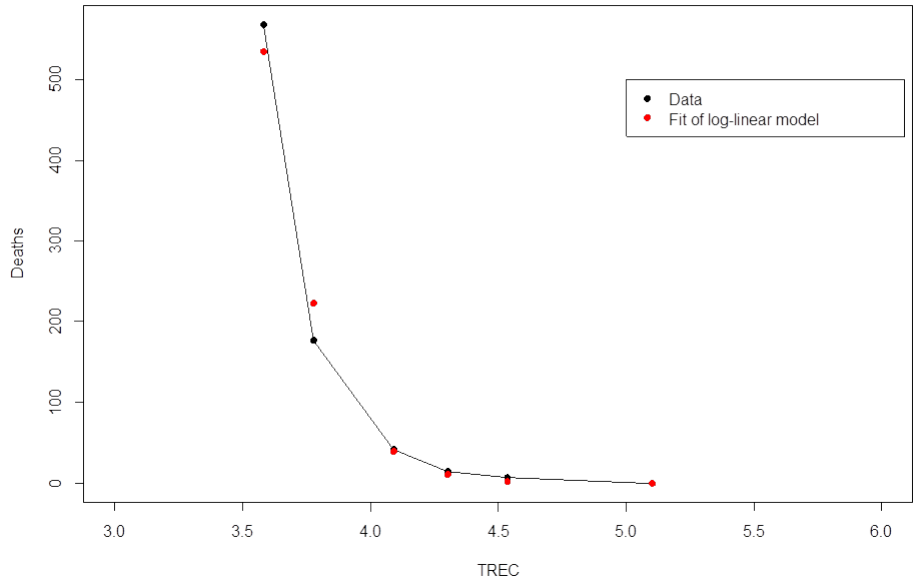

Figure 4: **A plot of average TREC amount in the blood amount vs number of Deaths, correlated over age**

	Hospitalizations			Admitted to ICU			Deceased		
Age groups	**To June 1 (%)**	**2-8 June (%)**	**9-15 June (%)**	**To June 1 (%)**	**2-8 June (%)**	**9-15 June (%)**	**To June 1 (%)**	**2-8 June (%)**	**9-15 June (%)**
≤ 19	1.0	2.1	2.0	1.0	2.6	0.0	0.0	0.0	0.0
20-29	2.6	3.8	2.0	3.7	5.3	0.0	0.1	0.0	0.0
30-39	4.4	5.1	5.2	4.6	0.0	15.8	0.2	0.0	0.0
40-49	7.5	6.4	7.8	9.8	10.5	21.1	0.5	0.0	0.0
50-59	13.8	14.9	16.3	20.4	15.8	15.8	2.2	0.0	8.2
60-69	16.8	18.3	12.4	25.0	23.7	26.3	6.9	9.5	6.1
70-79	20.8	17.9	20.9	24.0	26.3	15.8	18.1	19.0	10.2
80+	33.2	31.5	33.3	11.4	15.8	5.3	72.0	71.4	75.5
Gender									
Female	48.4	46.0	50.3	38.4	34.2	31.6	54.2	54.2	51.0
Male	51.6	54.0	49.7	61.6	65.8	68.4	45.8	45.8	49.0

Figure 5: **Epidemiological summary of case severity from the beginning of the outbreak to June 17th.** Source: WEEKLY EPIDEMIOLOGY UPDATE (11-17 JUNE, 2020), Public health Agency of Canada (PHAC) [3]

frequent interactions between two species competing for the same resources, there is an increased risk, especially in the presence of a respiratory virus, that a mutation can occur that renders the other species susceptible to a disease which is well tolerated in the donor species. As a consequence, our virome, the set of viruses that we tolerate and can carry with us, can be interpreted as a means of defence against an invading species which threatens our survival and competes with us for available resources. In the receiving species, it is those members who, for a multitude of reasons, are better able to sustain diversity in their immune repertoire who are favoured to have a mild clinical course. As diversity decreases with age, this species-level transmission clearly favors the young and those who have maintained hormonal and immune homeostasis. Furthermore, by the mere fact that the virus is well tolerated, it is plausible that these viruses have evolved for a number of years, under selection pressure, to be less harmful and as such are a fitness test. This test measures the ability to mount an immune response in the presence of rarely seen antigenic molecular patterns. Those members of the

species, incapable of maintaining an adequate and sustained diversity in their immune reservoir are quite possibly at higher risk of developing severe COVID-19, something which seems to be supported by all known risk factors.

3.6 Aging

It is impossible to not notice the obvious connection to aging which has a clear link to susceptibility, as shown in Figure 3. The link between aging and the thymus had been previously made [44] and it is the opinion of this author that the thymic output is a crucial element of the aging process, to be investigated thoroughly. While the bone marrow progenitors age as well, which essentially makes the T-cells less functional as they exit an aging thymus, it is clear that with thymic rejuvenation in combination with young stem cells may have the potential to better maintain a diverse and functional immune system. This being said, the nature of the selection process in the lymph nodes which favours specificity would need to be rebalanced in some way so that the new thymic emigrants would have the opportunity to make a meaningful contribution to this reservoir. As is, the selection process means that the thymic output is a means of increasing the bioavailability of the thymic diversity, however it would be more effective if that diversity could be maintained in an aged lymph node. There is no clear solution to this problem for the moment.

3.7 Alternative Hypotheses

3.7.1 Regulatory T-cells and self-antigens

An alternative hypothesis, consistent with the data is that the viral epitopes may produce clonal expansions of self-reactive clonotypes of T-cells. Some self-reactive clonotypes are known to be suppressed by regulatory T-cells[50]. These clonotypes would not only be rare in abundance under normal conditions but also be suppressed by regulatory T-cells which would also lead to a delay in activation and clonal expansion leading to the lymphopenia observed. This hypothesis seems consistent with the instances of Kawasaki syndrome occurring in the pediatric population affected by COVID-19 as a clonal expansion of self-reactive T-cells would cause disseminated inflammation in the absence of virally infected cells.

3.7.2 ACE2 Expression

It has been suggested that variations in ACE2 expression could be a causal link which makes children less susceptible. While it is true that children have less ACE2 receptors, the difference in expression is not significant enough to account for both the wide differences in susceptibility as well as the lymphopenia observed in the most severe clinical cases.

3.7.3 NK cells

Some Natural Killer cells are of thymic origin are also thought to become less diverse in function with age and may play a more dominant role in the initial cointainment of the viral inoculum in children [51, 52]. It could be that the increase in diversity and lack of maturation of NK cells in children is an asset in terms of SARS-CoV-2 susceptibility.

4 Conclusion

Further work needs to be done to elucidate the importance of thymic output to long term survival of the host. There has been some shift in the recognition of the importance of the thymus as individuals age, particularly in terms of its ability to preserve the immune response to novel antigenic fitness challenges such as certain cancers[44]. As we age, we develop a biased distribution of T-cell receptors in the periphery and as such, for probabilistic reasons, the successful presentation to an unused and rare clonotype is delayed. In the case of a zoonotic transmission, not only has there been selection pressure in the donor species rendering the disease less harmful but the fact that virus has not co-evolved with receiving species may contribute to the lack of efficient response.

The efficacy of thymosine-α-1-Fc (TA-1) in the recent clinical trial [30] may have been through the facilitation of presentation of antigens to rare T-cell clonotypes. The oligoclonal nature of the diversity in the aging lymph nodes and the low amounts of naive thymic T-cells produced relative to those maintained by recurrent viral infections such as Cytomegalovirus (CMV) has been suggested as one cause of this lack of diversity [26]. Furthermore, it is established science that the immune system becomes senescent in the elderly population and is less capable of mounting a vigorous response to novel viral challenges.

The availability in the blood of thymic emigrants is enhanced in a situation of lymphopenia where the relative abundance of thymic emigrants would be higher which would enhance the efficacy of TA-1 in a situation where there is a lack of diversity in the host-response. In addition, a novel pandemic requires multiple points of investigation including

non-pharmacological ones such contact-tracing[2, 1, 5], public health and epidemiological work as well as drug discovery[35] including both traditional methods and in some cases, machine learning.

Author contributions

Marc-Andre Rousseau came up with the original idea of associating thymic output with SARS-COV-2 outcomes , wrote the paper and did literary research, Leonid Chindelevitch contributed in terms of the data analysis of covid patients, inference and writing of the paper, Gary An helped with the literary review and helped edit and write certain sections and provided a clinical medical perspective. Lintao and Rahul provided helpful discussions and conducted literary review and helped write some sections, David Stephens helped with the analysis of TREC and susceptibility datasets available in the literature and helped to determine the inference that could be drawn, Irina Rish contributed to critical discussions and editing the paper.

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