Review

Why Creating Transmissible Microbial Interferon Factories May Bring a Promise of a “Golden Era” in Future Human and Animal Health

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Review

Why Creating Transmissible Microbial Interferon Factories May Bring a Promise of a "Golden Era" in Future Human and Animal Health

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Abstract: Transmissible microbial agents have brought utmost short-term and long-term concern for the public health sector due to the fact that they are generally highly capable of inducing serious consequences for the integrity of whole host organisms. Recently, it was discovered that the most important reason of their increasing capability and complexity of their immunopathogenesis capabilities represents their increased abilities of evading host immunity by undergoing direct and indirect levels of molecular self-camouflaging against host Pattern-Recognition Receptor, as well as the Type I and Type III Interferon-encoding genes. Clinical researchers developed medical approaches based on fairly low dosages of Type I Interferons for prophylactic and early therapeutic purposes against major infectious diseases like COVID-19, and the results were rather promising. Furthermore, scientists detected a high extent of immunostimulatory and immunomodulatory effects that such interferon glycoproteins bring upon the rest of the immune system. Essentially, they play a foundational role in the adequate activation of the immune system if they are produced in a timely manner. A developed medical approach against Diabetes Mellitus involving the exponential increase of the bioavailability of insulin via gene insertion into genomes of bacteria inoffensive to human and animal health may constitute a highly-matching model for the development of revolutionary vaccine candidates. Specifically, it may be important to consider the existence of candidate prophylactic and early therapeutic approaches implicating the allowance of environmental spread genetically-modified transmissible microbes with inserted human or animal Type I and/or Type III Interferon-encoding, as well as Pattern Recognition Receptor agonist protein-encoding genes that are attenuated on their genetic side responsible for induced pathogenesis and maintained pathophysiology, and perhaps not as much on their genetic side responsible for microbial reproduction and transmission. Perhaps, human and animal genes encoding recently-discovered fourth class of interferon glycoprotein can also be included in the equation of microbial gene insertion. Other genes that may also be included in such a context are the ones encoding bacterial outer membrane proteins that assemble the protollin immunostimulatory agent together with lipopolysaccharides, given that protollin plays a major role in the activation of various Pattern Recognition Receptors that are known as Toll-Like Receptors and could likewise count as a Pattern Recognition Receptor agonist. An overall approach as such ought to occur during the first days of the autumn season, when common cold- and flu-inducing viruses only begin to spread from person to person. The overall objective is to thoroughly fill in the gap of immune evasion, which may only be possible if Type I and Type III Interferons are automatically produced and signalled to neighbouring cells and tissues by the exact time the first cells become infected. If such a candidate approach is proven to be successful, it would indicate that several pathogenic agents would start undergoing a "Reverse Evolutionary" process that could ultimately even result in their natural de-selection, due to the fact that strategic allowances of such microbes to spread in the local environments would lead to the domination of such genetically-modified microbes against wild-type microbes, and also due to the fact that the human interferon systems would become increasingly sensitised and be situated in a novel evolutionary curve of growth in relation to such microbial agents. In short, following extensive scientific and clinical research efforts, it may now be possible to create and evaluate transmissible vaccine

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candidates that aim to create a firm bridge between innate and adaptive immunity and that could bring widespread and unprecedentedly beneficial effects for human and animal health.

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Introduction

Throughout history, microbial agents have caused various ravaging epidemics and pandemics, and in a number of cases, they have wiped large fragments of the population out. All microbial agents causative of such tragic public health incidents have implicated at least a considerable degree of induced immune evasion in the process of pathogenesis and extended pathophysiology. Likewise, all epidemics and pandemics have represented effects of specific evolutionary events within the microbial domains that implicated sudden natural selection against previous set of adaptation events within the host immune system. Such an aspect implies that evolutionary biology represents the foundational layer upon which the fight between the human immune system and various pathogenic agents have been occurring nearly since the beginning of the history of human civilisation. With regards to immunological functions, it is vital to highlight the important roles that each immunological department plays in the strive against microbial infection and for the integrity of the general state of health. The immune system consists of the natural and the adaptive immune systems, and each department plays unique roles in the maintenance of human health. Nonetheless, it has recently been demonstrated that both departments share commonalities in functions after all, despite initial projections in which the two immune systems played vastly distinct roles. For example, it has recently been shown that the natural immune system displays traits of adaptive immunity-like specificity and that it even displays its own “specific memory”. On the other way around, it has also been shown that the adaptive immune system displays natural immunity-like traits as well. Henceforth, the scientific argumentation that natural immunity-based vaccination is possible has been considerably fortified by recent evidence, and clinical researchers are now significantly encouraged to explore novel methods of natural immunity-based vaccination, alongside methods that involve a joint approach of natural and adaptive immunity-based vaccination. Importantly, recent clinical trial data has displayed particularly major benefactory roles that first-line and second-line, natural immune elements play in the determination of immunostimulatory and immunomodulatory activities that are proportional with the severity of various types of infections. Namely, human recombinant Type I Interferon glycoproteins have displayed colossal beneficial activities against major infectious agents if they were used for prophylactic and early therapeutic purposes. On the other hand, such immune agents have sometimes contributed to pathophysiology if they were used for the purpose of latter therapy and such incidents have been more prevalent in people with underlying health conditions, as well as with conditions involving autoimmunity and immune suppression, potentially showing that such interferon glycoproteins display “double-edge sword” like traits in their functionality, stimulating scientific researchers to emphasise upon the need for such immune protein to be solely evaluated as potential prophylactic and perhaps early therapeutic immunisation candidates (Carp T., Metoudi M. and Ojha V., 2024).

Unlike the first class of Interferons (IFNs), which were discovered just after the half of the 20th century, Type III Interferon glycoproteins have only recently been discovered as major immunostimulatory and immunomodulatory elements of the natural immune system that play shared roles with Type I IFN glycoproteins. Furthermore, a novel class of interferons - Type IV Interferons - has recently been discovered through genomic research procedures in zebrafish by

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clinical researchers from China (Su J., 2022). Given the fact that IL10R2 represents a receptor component that is also responsible for the synthesis of Type IV IFN glycoproteins, it is likely that they also play a major role in early immunostimulation and immunomodulation, alongside Type I and Type III IFNs (Chen S. et al., 2022). It is believed that candidate prophylactic and early therapeutic approaches would have effects analogous to the ones brought by Type I Interferons, although it is possible that more scientific evidence needs to be collected to confirm the extent of efficacy, as well as the comparison with the rates of efficacy displayed by the first class of Interferons. Nonetheless, it is essential to describe the tree of foundation constituted by the interferon system in the natural immune system. Namely, the first and the third class of interferons themselves constitute foundational factors for the extent of activation of the second class of interferons. Likewise, it may be important to regard Type I and Type III Interferons as pre-cytokine elements of the innate immune system, as they play a foundational role in the activation process of major cytokines, which represent products of Interferon-Stimulated Genes (ISGs), as well as of recruited Natural Killer (NK) Lymphocytes, which constitute factories for Type II Interferons once recruited as a result of interaction with ISG cytokines. ISGs are known to be component of cells containing the IFNAR1/2 and IFNLR1/IL10R2 interferon receptor complexes upon their surfaces, meaning that they can only be activated if Type I and Type III Interferon glycoproteins are effectively synthesised, exocytosed and transmitted to such cells. It is only when NK Lymphocytes are recruited and Type II Interferons are synthesised and signalled that the process of adaptive immune activation finally occurs via the recruitment of major subtypes of B- and T-Lymphocytes, with the synthesis of IgM and IgG antibodies, and the proportionality with the severity of the infection is ultimately determined by the proportionality of the activated Type I and Type III Interferon glycoprotein-based responses during the first stages of the infection. Any delays in the activation process of the first and the third classes of interferons may bring substantial consequences for the quality of the overall immune response, at least during the first part of the clinical disease. Likewise, it may be important for the scientific and clinical research communities to innovate novel, creative methods in which the interferon system is automatically sensitised when the pathogenic agents enter the first host cells. Such a step may play a major role, at least in transforming common cold and flu-like diseases from incurable diseases to eradicable ones. Clinical testing of such hypothesised approaches may be crucial to ensure that all guidelines established by scientific and medical ethics are respected to the letter.

Discussion

The process of bacterial gene editing via CRISPR-Cas9 to transform inoffensive bacteria into factories for human insulin represented a revolutionary approach for the widening of treatment against Type I Diabetes Mellitus, and it has saved millions of lives worldwide as a result, given the fact that before such a medical update, insulin had very limited availability for patients with the disease, which left entire third-world populations at imminent risk of death following crises of the disease. Such an updated clinical approach involves the isolation of certain, harmless bacteria that include Escherichia coli, the extraction of bacterial genetic material into a plasmid, via the utilisation of specific restriction endonucleases, the addition of a human gene encoding insulin into the plasmid via the utilisation of distinct restriction endonucleases, prior to the insertion of the modified plasmid back into the bacterial genome, which is located in the nucleoid of the prokaryotic cell. It is possible that such gene editing is applicable for infectious viruses, and that scientific researchers are capable of transforming pathogenic agents in factories for the most fundamental and important immune proteins. It is important to acknowledge the fact that microbial agents utilise direct and indirect methods of molecular self-camouflaging, which indirectly and directly target the sensitivity of Type I and Type III Interferon-encoding genes (INGs), respectively. Namely, direct methods of microbial self-camouflaging involve the double methylation of the 5′ end of viral genomes by the viral non-structural protein (NSP)-based NSP10/14 and NSP10/16 methyltransferase enzymes respectively, which altogether prevent the activation of various Pattern Recognition Receptors (PRRs), making the host cells unable to detect Pathogen-Associated Molecular Patterns (PAMPs) and Damage-

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Associated Molecular Patterns (DAMPs), indirectly but still considerably affecting the activation rate of such INGs by causing the host cell to fail in distinguishing pathogenic genetic material from cellular genetic material, for example. In such a case, NSP10 represents the activator component of the enzyme complexes, whilst NSP14 and NSP16 represent the effector components of each complex respectively. Indirect methods of microbial self-camouflaging, on the other hand, are generally aimed at directly inhibiting the synthesis of Type I and Type III Interferons, as well as of ISG cytokine products, broadly via the synthesis of NSPs 1 and 2, potentially affecting the overall process of immune activation in a severe manner. Another indirect method of microbial self-camouflaging that directly antagonises the interferon system and that may severely impact the quality of the immune response is the rapid distribution of non-structural proteins via the utilisation of tunneling nanotubes (TNTs) produced by cells with the initial purpose of the rapid distribution of healthy signals to neighbouring cells, including of Type I and Type III Interferons in case infection occurs. Due to the fact that PRRs are also targeted in the process of pathogenic immune evasion, it may also be essential to include genes encoding agonist proteins for various human PRRs in the list of potential genes included in such a CRISPR-Cas9-based candidate procedure. Where limitations of gaps in the any process of induced effect of herd immunity without any harm produced exist, perhaps as a result of the powerful antimicrobial immunogenic effects induced by Type I and Type III Interferon glycoproteins, inhalators and injectable sera containing low dosages of such transmissible factories for Type I and Type III IFNs, perhaps alongside PRR agonist proteins, could also be produced and distributed. Where needed, microbial genes responsible for induced pathogenesis and maintained pathophysiology can be pronouncedly attenuated, whilst perhaps keeping the genes responsible for microbial reproduction and transmission unaltered. The objective of such an overall set of clinical candidate approaches is to transform microbial agents into harmless factories for the Type I and Type III Interferons, which represent the fundamental activators of the immune system during infectious exposures.

Results of several clinical testing procedures that include double-blinded clinical trials have shown that low dosages of human recombinant Type I and even Type III Interferons display high rates of efficacy in the prophylaxis and early treatment of various infectious and oncological diseases that include SARS-CoV-2-induced COVID-19, H1N1 and H5N1 Influenza A Virus (IAV)-induced flu-like diseases, HIV-1-induced AIDS, Rhinovirus, Human Metapneumovirus and Parainfluenza Virus-induced common cold diseases, Monkeypox, as well as Hepatitis B Virus-induced tumours and hepatic melanoma, respectively. Furthermore, it has been hypothesised that cells of natural immunity that include NK Lymphocytes, and especially central elements of adaptive immunity that include helper CD4+ T-Lymphocytes and cytotoxic CD8+ T-Lymphocytes can be inoculated with a low dosage of recombinant, glycosylated Type I and Type III Interferon and have both their levels of integrity and of functionality considerably increased. Such an aspect may represent a crucial detail for the research efforts aimed at developing prophylactic and perhaps early therapeutic approaches against AIDS, for example. In short, such an approach could represent an immunisation process occurring within immunising agents, and even involve the transformation of regular innate and adaptive lymphocytes into “super-lymphocytes”, potentially representing a major step in the development of a counter-evolutionary approach against various microbes of public health concern that would not have a precedent in the history of vaccine development and of public health. Interestingly, plasmacytoid dendritic cells (pDCs), as well as Type I and Type III Interferon glycoproteins, are situated in a relationship of mutual, bilateral support, due to the fact that pDCs constitute primary producing factors for such interferon glycoproteins, and that simultaneously, such interferon glycoproteins are signalled to pDCs with the purpose of sensitisation to the presence of infectious agents and perhaps also to sharpen their integrity and optimise their immune functions. Furthermore, it has recently been determined that a substance known as protollin bring effects similar of Type I and Type III Interferon glycoproteins following its nasal administration, recruiting adaptive lymphocytes to the encephalon, which in turn activate microglial cells and likewise contributes to the prevention of a process of astrocyte deposition that is known as astrogliosis, as well as in a process

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of destruction of soluble and insoluble beta amyloid plaques in patients that are about to develop clinical Alzheimer's Disease (Frenkel D. et al., 2008). Furthermore, it has even been indicated that protollin brings immunising effects against Alzheimer's Disease, which further indicates the significant level of functional similarity with Type I and Type III Interferons (Frenkel D. et al., 2005). Interestingly, it was discovered that protollin plays a visible role in the activation of Toll-Like Receptors (TLRs), which represent major types of Pattern Recognition Receptors (PRRs), and it is known that PRRs represent important activating factors for Type I and Type III Interferon-encoding genes (INGs), potentially meaning that protollin represents a relevant example of PRR agonists (Jones T. et al., 2004). Likewise, it may be possible for a joint immunisation candidate approach involving such interferon glycoproteins and protollin to be utilised against various infectious and non-infectious diseases. Moreover, it may be hypothesised that innate and adaptive lymphocytes can be treated with a low dosage of the protollin immunostimulatory and immunomodulatory agent as well, potentially making immunising and therapeutic effects even stronger, more durative and able to cover more diseases. Perhaps, genes encoding the proteins of bacterial outer membranes that assemble the protollin substance alongside lipopolysaccharides (LPS) could also be included in the list of genes that could be inserted into viral and bacterial genomes to automatically stimulate the activation of the immune system by the time the first infectious event occurs.

Applications of such candidate immunising approaches may cover a high diversity of infectious diseases and modern-day problems regarding evolved microbes. For example, such a potential update in vaccine innovation and development may even impact the dilemma of acquired single-drug and multidrug antibiotic resistance by pathogenic bacteria causative of major clinical disease. It is known that vaccine development and phage-based therapy represent two major alternative clinical pathways against antibiotic-resistant bacteria, potentially meaning that major updates in vaccine-based research could implicitly weaken antibiotic-resistant bacteria and aid in the prevention of several clinical cases of diseases induced by such adapted microbes. Furthermore, it may be important to utilise up-to-date precision methods in the determination of the initial phases of seasonal outbreaks of common cold and flu-like infectious diseases, which are most statistically probable to occur, on average, around the second week of the month of September in the Northern hemisphere, as well as around the third week of the month of March, on average, in the Southern hemisphere. Furthermore, it may be important to include specific Artificial Intelligence models designed for the accurate mathematical and statistical determinations of the peak probabilities regarding the first stages of the spread of various infectious diseases, as well as regarding specific prophylactic and early therapeutic approaches against such infectious diseases. Specifically, certain AI models could be adapted to computer programs, including Microsoft Excel and SPSS, that comprise mathematical and statistical models, which in turn can be applied to genomic sequencing and virtual assembly of various microbial and immunological phylogenetic trees, which are normally performed through various online databases that include EMBOSS Needle's Pairwise Sequence Alignment, as well as Clustal Omega's Multiple Sequence Alignment, with the overall purpose of automating the process of statistical projections and only leaving the process of data entry manual for attentive human work. Two major areas of integrated AI model-based catalysis of research could involve the thorough analysis of phylogenetic trees covering genes that encode major areas of human and animal immunity that include the interferon system, and particularly Type I, Type III and Type IV Interferons, and microbial genes known to directly or indirectly antagonise the activity of genes that encode such interferons, as well as processes of statistical projection estimating levels of safety and efficacy displayed by pharmaceutical approaches based on such elements of the interferon system. The overall objective of such implementations into immunological and microbiological research is to determine a higher resolution of details, increase the speed of the scientific scrutiny, and reduce probabilities of errors in major data findings. If such AI models are successfully implemented and specifically applied to the contexts of modern-day evolutionary microbiology, evolutionary immunology and public health sciences, it may become increasingly more probable for such novel AI models to build relatively accurate statistical projections regarding the occurrence of

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certain epidemics and pandemics in the future, as well as the development of specific prophylactic and early therapeutic approaches that could be specifically efficacious or even revolutionary. Recently, the Sonic Healthcare UK Health Corporation has developed an AI model known as franklin.ai in order to help medical laboratories extend the capacity of online databases holding results of various laboratory tests offered to general hospital patients to assess whether markers for various diseases are present or not. Such developments are deemed as safe due to the fact that a voluminous extent of automation has been involved, making risks for GDPR data breaches or protection of the database against various informatic hazards pronouncedly low (Carp T., 2024).

Conclusion

Recent public health crises have substantially motivated entire scientific and research communities to profoundly and consistently research for potential updates in modern-day therapeutic and immunising approaches to further aid human and animal immune systems in overcoming various polymorphic infectious agents without undergoing levels of immunopathogenesis and maintained immunopathophysiology that are deemed as threatening to the state of health. With the recent occurrence of the SARS-CoV-2-induced COVID-19 pandemic, the number of scientific procedures, experiments and pieces of literature review has visibly increased, with novel concepts in natural and adaptive areas of immunology having been discovered, almost on a daily basis. The novel era of digitalisation and implementation of AI models has also contributed to an effective catalysis and improvement of quality of scientific and clinical research covering both the microbiome and the immunome, and it is potentially helping scientists fill in major gaps in prophylaxis and therapeutics against polymorphic microbe-induced diseases in a quicker manner whilst becoming less likely to accidentally produce errors in the research process. The research domains of immunology, pharmacology and medicine have been situated in a constant chase for the discovery of medical approaches that could all together constitute the perfect “missing piece of puzzle” that would lead to the eradication of various life-threatening and incurable illnesses in both humans and animals. Such a chase for potential breakthrough has been regulated by the existence of rigorous bioethical guidelines that likely filters numerous candidate medical approaches out of the list of safe and efficacious clinical responses against diseases of individual and public health concern. Due to the exponential increase in the availability of scientific and medical information, as well as the progressively wider applications of Artificial Intelligence into various scientific platforms and search engines, it has become increasingly possible for mankind to find the proportionate recipe for prophylactic and therapeutic approaches that may lead even several pathogenic agents into a “Reverse Evolution” process that could effectively bring them to an irreversible stage of natural deselection. Such a scenario constitutes the ultimate objective of modern day immunological research, as clinicians are situated in a rush to detect methods of attenuating and even cancelling the processes of induced immune evasion that implicates a transient prevention of the activation of first-line and second-line, natural host immunity. Ultimately, the overall process of clinical response against major infectious diseases ought to be as proportional to the extent of immune hijacking by the causative infectious agent as clinically possible.

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