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Review

Alpha-Synuclein Dysregulation in Systemic Pathophysiology of Synucleinopathies

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Abstract

Alpha-synuclein (α-syn) has long been identified as the etiologic agent of multiple neurodegenerative diseases, the most common and well-known of which are Parkinson's disease (PD) and Lewy body dementia (LBD). While it is known that the pathophysiology of these synucleinopathies involves aggregation of improperly-folded α-syn, the mechanisms leading to its accumulation have not been fully identified. However, multiple pathways have been proposed, any or all of which may contribute to synucleinopathies. The role of α-syn in normal homeostasis and in other organ systems, especially the hematopoietic system, has been reported recently. Research within the last decade has shown that α-syn plays many vital and conserved roles in the cell biology of various organ systems, such as packaging of cell products, exocytosis, membrane stabilization, and more. This protein has been recognized as an essential factor in normal hematopoietic and immune systems function, and its deficiency leads to an abnormal phenotype, in hematopoietic and immune cell lineages. Similar phenotypes in synucleinopathies not only emphasize the conserved nature of the synuclein family but suggest a bimodal pathophysiology in which aggregated α-syn leads to cellular toxicity while causing derangement of systems that require it. Research into specific molecular mechanisms and potential treatments may provide further understanding of neurodegenerative diseases as well as lead to novel therapies. However, elucidation of the systemic roles of α-syn in addition to its toxicity in excess is essential to prevent treatment-induced deprivation, which paradoxically harms the patient. Here, we address recent advances in systemic synucleinopathies and putative interconnectedness of these compartments. While previous studies and reviews have focused on the mechanisms of α-syn synthesis, transport, and aggregation within systems, this review focuses on the potential inter-systemic nature of synucleinopathies and their possible synergistic origins.

Keywords: α-synuclein; synucleinopathies; neurodegenerative disease; Parkinson's disease; hematopoiesis; immunity

1. Introduction

Alpha-synuclein (α-syn), a member of the synuclein family of proteins, is a small protein with highly-conserved sequences and three well-studied domains [1,2]. It is ubiquitous throughout the human body, and its integral roles include membrane fusion, endocytosis, and exocytosis, including within non-neuronal cells, especially red blood cells (RBCs) and platelets [3–5]. Aggregates of α-syn have also long been identified as a driver of a family of progressive, degenerative central nervous system (CNS) diseases known as synucleinopathies, most famously Parkinson's disease (PD) but also encompassing Lewy body dementia (LBD) and multisystem atrophy (MSA) [6]. Especially within the last two decades, multiple mechanisms of α-syn-mediated neurodegenerative diseases (NDD) have been and continue to be both proposed and researched. However, despite its role in multiple organ systems, research into the role of α-syn in non-neuronal, peripheral and/or hematopoietic pathophysiology has been relatively unknown until recently.

Since the hematopoietic system requires endogenous α-syn for normal function, new efforts to establish the pathways mediated by α-syn in both hematopoietic function and dysfunction have been undertaken. For example, RBCs account for the majority of circulating α-syn, while platelets exhibit a higher protein fraction of α-syn [7,8]. Indeed, widespread presence of α-syn across cell lineages of the hematopoietic system implicates that it is important in almost every cell line [4,9–11]. This protein is particularly essential to the structure and function of immune cells. Both systemic deficiency of α-syn and its aggregation in neural tissue have been associated with significant T-cell dysregulation [10,12], implying that when α-syn is predominantly present in aggregates, its presence in the hematopoietic system can be affected. This suggests that α-syn-associated systemic pathophysiology within the CNS can be seen as bimodal in nature: excess of α-syn in aggregates and paucity of α-syn, also known as the synucleinopenia hypothesis [13], may both contribute to disease.

Other systems that are affected by synucleinopathies, some of which have been implicated in CNS disease, include the gastrointestinal (GI) tract and the integumentary

system; in this regard, the gut microbiome and its interaction with α-syn have been postulated as a potential point of origin for neurodegenerative synucleinopathies [2,14]. If true, these hypotheses correlate with recent research suggesting that the gut microbiome is highly connected to the nervous system via the "gut-brain barrier", and with ever-increasing evidence that multiple systems could contribute to mechanisms influencing neurologic disease as a whole.

In summary, contrasting with the prevalent view of α-syn-induced disease as primarily neurological, potential molecular mechanisms in which different systems cause and are affected by α-syn dysregulation have been identified. Although the structure and function of α-syn are well-studied, much work will still need to be done regarding its interaction with non-neuronal systems in which it is necessary and those in which it is detrimental.

2. Alpha-syn Structure and Function

Alpha-synuclein is a protein consisting of 140 amino acids with highly evolutionarily conserved sequences, which it shares with the beta- and gamma- isoforms in the same family, and three domains that include two regions considered important in disease: the N-terminal and the C-terminal regions, and a central region between them [1,15]. The N-terminal region is primarily alpha-helical in nature and is highly important in lipid binding (membranous structures). Conversely, the C-terminal region has a wider range of actions that include post-translational cellular modifications, protein chaperoning at synapses, and docking of protein complexes; this region is also thought to prevent aggregation in its usual conformation [16]. Multiple methods of post-translational modification of α-syn have been identified and studied, with phosphorylation predominant in normal function as well as preventing aggregation [1,17]. Additional common post-translational modifications include proteolysis/truncation, oxidation, glycation, and ubiquitination, although phosphorylation is the best-known of these mechanisms and appears highly necessary to retain characteristic protein flexibility [1,17].

The configuration of α-syn is largely dependent on the membrane and/or cell type to which it binds; it is commonly found in an alpha-helix configuration when binding to lipid membranes and in a broken alpha-helix when binding to small vesicles [17]. While its relative structural flexibility lends itself well to membrane trafficking, packaging, and transport, these same characteristics—especially in the C-terminal region—cause α-syn to easily misfold and subsequently form aggregates [4,17,18]. Specifically, β-helical configurations have been identified as most pathologic [18]. These aggregates have long been implicated as the major drivers, if not the root cause, of synucleinopathies such as PD and LBD [17–19].

There is also evidence that α-syn contributes to mitochondrial function, particularly in neurons, which could in turn contribute to NDD pathology [20]. Additionally, interaction of α-syn with cytoskeletal proteins may both contribute to understanding of its full function and provide an alternate mechanism by which it causes neurodegenerative pathophysiology [21]. The many roles that this protein plays in normal homeostasis provides ample avenues for future research. In the following sections, tissue-specific α-syn utilization will be discussed.

2.1 The Hematopoietic System

While research into α-syn has traditionally focused on the neurologic system, it has been found that it is important, if not essential, in the majority of the hematopoietic system. Certain categories of cells are predominant in usage and production of this protein. As previously mentioned, RBCs produce α-syn and require it for differentiation [4,5,9,22]. Within the erythrocyte compartment of the hematopoietic system, it has been found that α-syn is expressed as early as the erythroblast stage, as confirmed by immunohistochemical staining of bone marrow; staining is most evident in erythroblasts [5]. α-syn is upregulated concurrently through maturation with other maturity-marking proteins, such as hemoglobin subunits [22]. While erythrocytes are anucleate, early erythrocyte precursors require α-syn-associated cell membrane function for effective maturation, including the aforementioned hemoglobin expression and the later physical process of nucleic acid expulsion [5,23]. Changing localization of α-syn on nuclear membranes (early development) and in the cytoplasm (most prominent in later maturation) provide evidence of its necessity; it is, unlike many proteins, upregulated rather than downregulated with increasing maturation [22]. It is furthermore upregulated by GATA-1, itself a prominent protein in RBC maturation [23]. Additionally, α-syn—through its widespread membrane-binding functions including binding to phosphatidylserine—appears essential to characteristic RBC membrane fluidity and flexibility, and likely binds to proteins such as transferrin, which are essential to iron homeostasis and processing [7,22].

While not the only driver of platelet function, α-syn is present in platelets and regulates α-granule release, acting not only as a chaperone in platelet function but also as a calcium-dependent negative regulator that prevents excessive platelet activation; also, it is present as early as the megakaryocyte stage [3,24,25]. Mechanistically, these findings are likely due to the necessary interaction of α-syn with cell-surface receptors partially responsible for platelet aggregation, such as glycoprotein Ibα [26]. Platelets, although anucleate like erythrocytes, additionally express vesicular and target soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) proteins, with which α-syn likely interacts to achieve optimal conformation and allow the release of granule contents. Such functions have been identified in cells within multiple systems and lineages [4]. This suggests a role in multiple phases of platelet activation, suggesting that α-

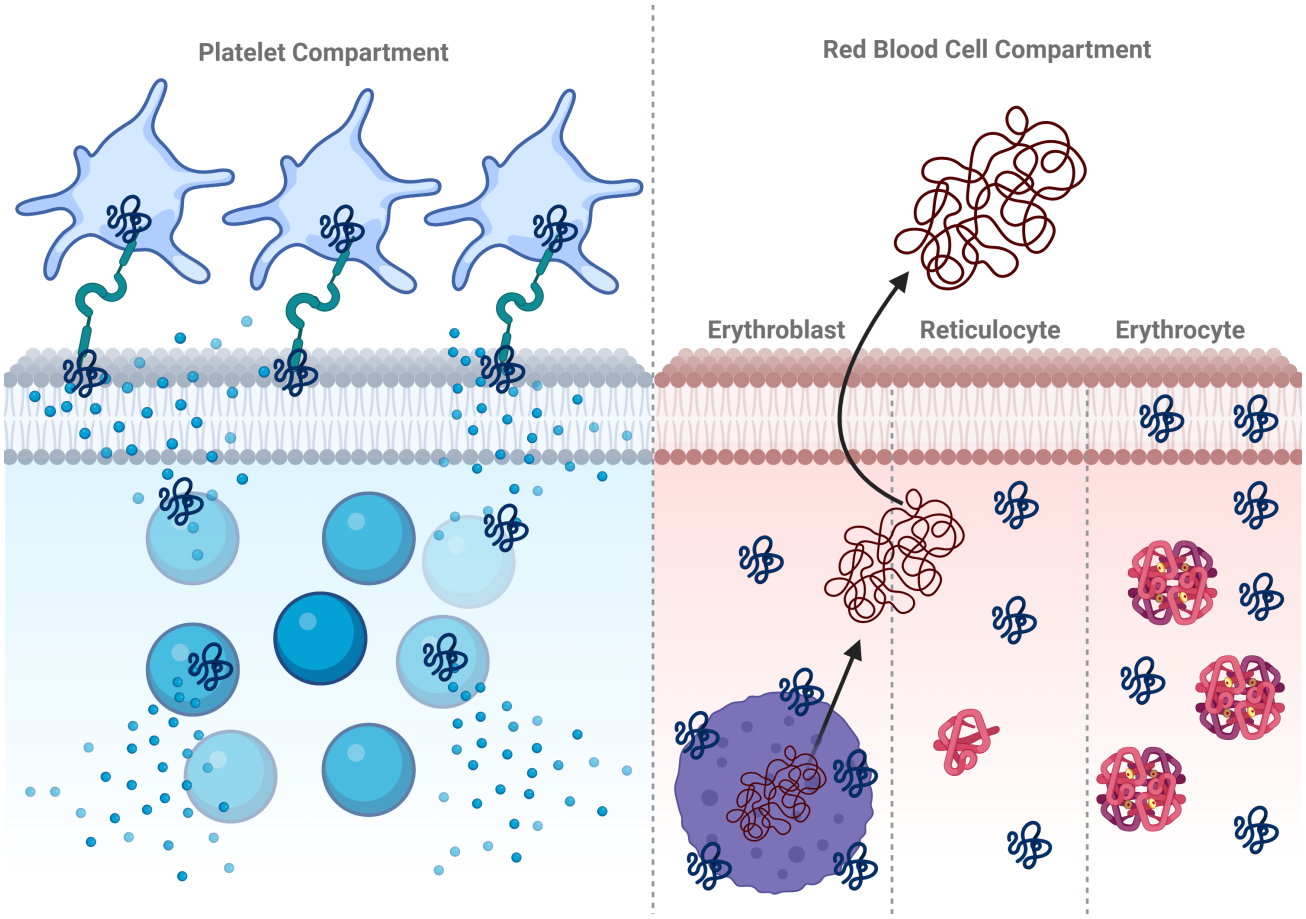

Fig. 1. Hypothesized pathways and functions of alpha-synuclein in platelet and red blood cell compartments. Depiction of the use of alpha-synuclein in platelets (left) and red blood cells (right), including aggregation, membrane integrity, and expulsion of genetic material and granules into the bloodstream and surrounding tissues are depicted. Created with BioRender.com.

syn may be necessary throughout the activation process [7]. For instance, α-syn deletion in combination with the protein multimerin-1 has been shown to contribute to bleeding diathesis [26]. Furthermore, α-syn continues to be released even after platelets have been extracted from whole blood and stored, which provides insight into a potentially more dynamic purpose within the megakaryocytes and platelets themselves [7]. These roles appear to be not dissimilar to those in the erythrocyte compartment (Fig. 1).

Lack of α-syn significantly dysregulates the immune response within almost all leukocyte categories, and as such its roles have been at least partially described. Its deficiency prevents normal maturation and function of both the innate and adaptive immune systems. Differentiation and effective phenotype switching of macrophages and dendritic cells are significantly decreased, as is their subsequent antigen presentation [27]. Within the adaptive immune system, α-syn deficiency changes and/or decreases the morphology, regulation, differentiation, and granule release in B and T cells, which shows not only that its release is essential to cell signaling, but that its membrane interactions are necessary for normal cell differentiation and physiological response [4,10,27,28]. Finally, impaired immunoglobulin G (IgG) production and B-lymphopenia in α-syn knockout mice emphasize the fundamental importance of this protein across multiple lymphoid compartments [11].

2.2 The Nervous System

The nervous system, perhaps the most commonly studied bodily system in this context, requires properly-functioning, un-aggregated α-syn to produce synapses. Its interactions with, particularly, presynaptic elements of a synapse is especially prominent in the dopaminergic, catecholaminergic, and glutamatergic neurons, all of which are largely excitatory in nature; this is anatomically readily detectable in the substantia nigra and locus coeruleus [17,21,29]. In terms of the nervous system as a whole, α-syn has historically been considered largely brain-specific, although its extensive role in the enteric nervous system will be explored later [1]. As this review describes, the prevailing view of α-syn-driven disease as brain-based with only marginal contributions from other systems is, given the results of a growing body of literature, likely outdated and should perhaps be set aside in favor of an inter-systemic

approach. However, α-syn remains the agent of synucleinopathies in the nervous system and its aggregation can occur and/or perpetuate there, which means that a thorough understanding of its mechanisms in the CNS should still be foundational in its study.

As synapses are largely driven by membrane- and vesicle-based interactions between neural cells, native α-syn in its membrane-binding and membrane-stabilizing capacities is vital for normal brain function. α-syn binds to and stabilizes cell membranes' lipid bilayers, maintaining the physical membrane structures that maintain cell and vesicle integrity as well as interacting with cytoskeletal proteins [1,16]. Via interactions with SNARE proteins and vesicle-associated membrane protein 2 (VAMP2), both terminal domains participate in synaptic vesicle docking and trafficking and localize largely within presynaptic vesicles [16,18,30]. This leads to well-known synapse mechanisms, in which, most commonly, vesicles containing neurotransmitters complete their actions at the postsynaptic terminal. However, α-syn is not limited to simple synaptic membrane interactions. It has been shown to help form fusion pores involved in the egress of cell contents, and binds to calcium, itself involved heavily in synaptic transmission and neuro-electrical impulses [16]. The mitochondria, which form vesicles as part of normal maintenance, attract α-syn, which has been linked to organelle degradation and damage following normal interactions [18,20]. In short, the widespread necessity and localization of α-syn in the CNS is consistent with its presence and roles in other systems.

2.3 The Gastrointestinal System

The nerve plexuses that drive visceral innervation and peristalsis, known as the enteric nervous system (ENS), require α-syn to function. This protein has been found to be distributed in the jejunum within both the neurons of the ENS and the epithelial cells [31]. Within the colon, it is present in both the muscular wall and the ENS, with some evidence that α-syn accumulation in these regions is a normal part of aging or reactive pathology rather than simply a harbinger of pending NDD [32,33]. In addition to this role, α-syn can stimulate the GI tract's immune function, allowing recruitment of immune cells to the gut during gastroenteritis [34,35].

In mice, it has been shown that α-syn is likely required for healthy development of the ENS, especially in terms of cholinergic neurons. For example. deficiency leads to evidence of poor colonic function, including constipation [36]. Interestingly, these symptoms are similar to constipation seen in PD patients, further indicating that disease is induced by both paucity and excess of α-syn and implying that tight regulation of its expression is important [37,38].

Outside of the gut, α-syn may play a part in normal function of other organs within or associated to the GI system, including the pancreas. Deletion of the protein causes a diabetes-like phenotype in mice, while overexpression improves glucose tolerance and insulin sensitivity, possibly through the same transport mediators involved in membrane trafficking [39]. It has also been described that there is a connection between α-syn and insulin resistance; since physiologic levels of α-syn prevents excess insulin secretion by modulating release of insulin granules [39,40]. Nevertheless, the co-occurrence of PD and diabetes, while not enough to determine causation, suggests that the same inflammatory mechanisms may play active roles in both etiologies, especially in the context of gut dysbiosis [40]. It should be noted that the changes in microbiome associated with diabetes, such as a decrease in short-chain fatty acid-producing bacteria, may themselves be independently associated with increasing metabolic and inflammatory derangement within the gut [41]. Given the frequency of diabetes in developed countries, potential synergistic interaction with α-syn-associated inflammatory mechanisms—especially with age, as α-syn increases systemically with aging—presents a potential area for further study [18,20,32,33].

3. Cross-System α-syn-Induced Pathophysiology

Oligomers, multimers, and fibrils are known to form as the result of abnormal α-syn aggregation. However, of these oligomers are thought to be the most toxic and to contribute most frequently to NDD, although fibrils are also frequently found and may precede multimers formation [4,19,42]. It is widely agreed that the tendency of α-syn to aggregate is caused partially by the mercurial conformation of its C-terminal component, which allows the protein to fold abnormally with relative ease [17,18]. While this single characteristic is largely, although not solely, responsible for the ability to form aggregates, likely multiple mechanisms are involved in the actual process. Phosphorylation, for example, appears to play a part in changing the protein's conformation [2]. Interaction with lipid membranes, one of the crucial functions of α-syn, may itself promote aggregation by changing the protein's conformation during normal physiologic interaction [43,44]. Post-translational modification may also contribute to this process [1,44]. Additionally, other risk factors may be environmental, such as heavy-metal toxicity, pollution, or even exposure to pesticides [40,45].

Once misfolded, these α-syn aggregates spread throughout affected systems in a prion-like manner, converting normal α-syn to the abnormal form potentially by hijacking normal vesicle function [19]. Initially, α-syn aggregates themselves cause intra-neuronal toxicity and neuron degeneration [42]. Attraction of the immune system to these—in effect—foreign bodies then create much of the early trigger and subsequent pathology characteristic of NDD. CNS-specific macrophages, known as microglia, generate a powerful inflammatory response locally that recruits both astrocytes and a myriad pro-inflammatory ele-

ments from the blood, many of which are α-syn-specific, that further damages neural tissue [18,42,46]. Additionally, lysosomal dysfunction, leading to inability to degrade α-syn aggregates, may represent another potential contributor throughout the entire process [47,48].

The effects on the CNS of α-syn derangement in the blood provide clues as to how the immune system, when deprived of sufficient α-syn as aggregation disseminates, contributes to NDD patients' physical and mental decline. It has been reported that α-syn is important to type 1 interferon signaling, an important initiator of immune signal transduction, within the nervous system [49]. Likewise, binding of lymphocyte activation gene-3 expands α-syn aggregate formation and toxicity, which suggests that pathologic interaction between α-syn and the adaptive immune system contribute to NDD; and excess α-syn may similarly activate the immune system to attack neural tissue [12,27,50]. Immunosuppression has also been correlated with NDD, potentially via loss of normal T-cell regulation preventing α-syn aggregation, although a definitive causative relationship has not been proven [51]. Moreover, although active T cells are increased in these diseases, overall T cell numbers are paradoxically decreased [12]. These findings emphasize that not only is the immune system in effect weaponized to perpetuate NDD, but its dysfunction can contribute to or possibly even initiate these disease processes.

Different origins of α-syn, and mechanisms of its transport into the CNS, have been proposed in recent years. With the rise in our understanding of the relationship between gut health and human health as a whole, concomitant understanding of the relationship between the gut and α-syn pathology has similarly increased. These relationships, i.e., "the gut-brain axis", have led to increased focus on the gastrointestinal system as one area of research for NDD, with the microbiome drawing increasing focus [52]. However, multiple potential avenues must be considered (Fig. 2).

3.1 Gut-Modulated α-syn Pathophysiology

As previously described, α-syn is present in relatively high quantities throughout the gut, primarily in the ENS but also within muscle and epithelium [31–33]. It is therefore a prime candidate to interact with elements of the gut, including the microbiome. Detrimental changes in the gut microflora typically involve decrease of normal commensals, such as *Bacteroidetes* [52], in favor of species that are typically less common, such as those in the *Bacillota* phylum [39]. Microbial changes dysregulate the immune response and disrupt normal gut homeostasis, including but not limited to development of colitis and inducement of α-syn aggregation [14,45,52]. In fact, amyloid produced by certain gut bacteria, known as "curli", can promote α-syn aggregation as well [53]. More recently, several groups have provided more evidence for gut-first synucleinopathy. A new study demonstrated the combined influence of α-syn and tau in gut-first NDD [54], while a separate paper provided neuropathologic evidence of Lewy body disease for gut-, or body-first, patients in a caudo-rostral pathology [55].

The connection between the gut and the brain is not linear, and bidirectional interactions cannot be ruled out as potential contributors to synucleinopathies and NDD [19]. A single mechanism has not been definitively identified at this point, but multiple potential pathways have been proposed. Of note, with an ever-increasing amount of knowledge about the gut, the microbiome and its proteome, and crucial interactions between the body and bacteria, research has continued to expand on this area. However, transport of α-syn in the blood can be both beneficial to hematopoiesis yet harmful to the body. On the other hand, α-syn aggregation and genesis of disease within the CNS, at least partially, also cannot be ruled out.

3.2 Proposed Pathways and Initiating Factors

The latest research regarding how α-syn may move from non-neural systems to the brain can be summarized with the terms "brain first" versus "body first" or "gut first", i.e., spontaneous generation within the CNS or nearby nerves as opposed to extra-neural aggregation followed by secondary transport to the CNS [2,56,57]. These categories are, of course, discrete and generalized, but are still useful in this context. "Brain first" has been and continues to be studied, while "body first" composes much of the current research into synucleinopathies, but neither potential pathway can be discounted. In fact, the connections between the central and peripheral nervous systems, and their subsequent intertwining with non-neural bodily systems, make elaboration of both general categories both complex yet necessary.

Within the "brain first" category, the olfactory nerve or bulb (OB) is considered potentially crucial in genesis and/or transportation of α-syn aggregates. Reports have shown that α-syn has been detected in the OB prior to onset of NDD symptoms, particularly motor ones [40,58]. Likewise, non-human primate experiments have shown that seeding the OB with exogenous α-syn leads directly to an artificially-induced NDD [59]. Rapid eye movement sleep behavior disorder, associated with excess α-syn in the area, is correlated with later development of NDD [56,60]. Additional potential sites for α-syn propagation include the dorsal motor nucleus, nucleus ceruleus, and amygdala, all of which are considered part of the CNS [2].

The gut-first paradigm, or gut to peripheral nerve pathway, is a strong candidate for an NDD genesis point within the "body first" category [57]. This hypothesis posits that following α-syn aggregation within the gut, likely as a result of gut dysbiosis and/or inflammatory disease, aggregates travel up the vagus nerve to the CNS [18,37,61]. The vagus nerve is likely not the sole pathway in this mechanism, but the autonomic nervous system (ANS)—of which the vagus nerve is a part—and its associated organs appear

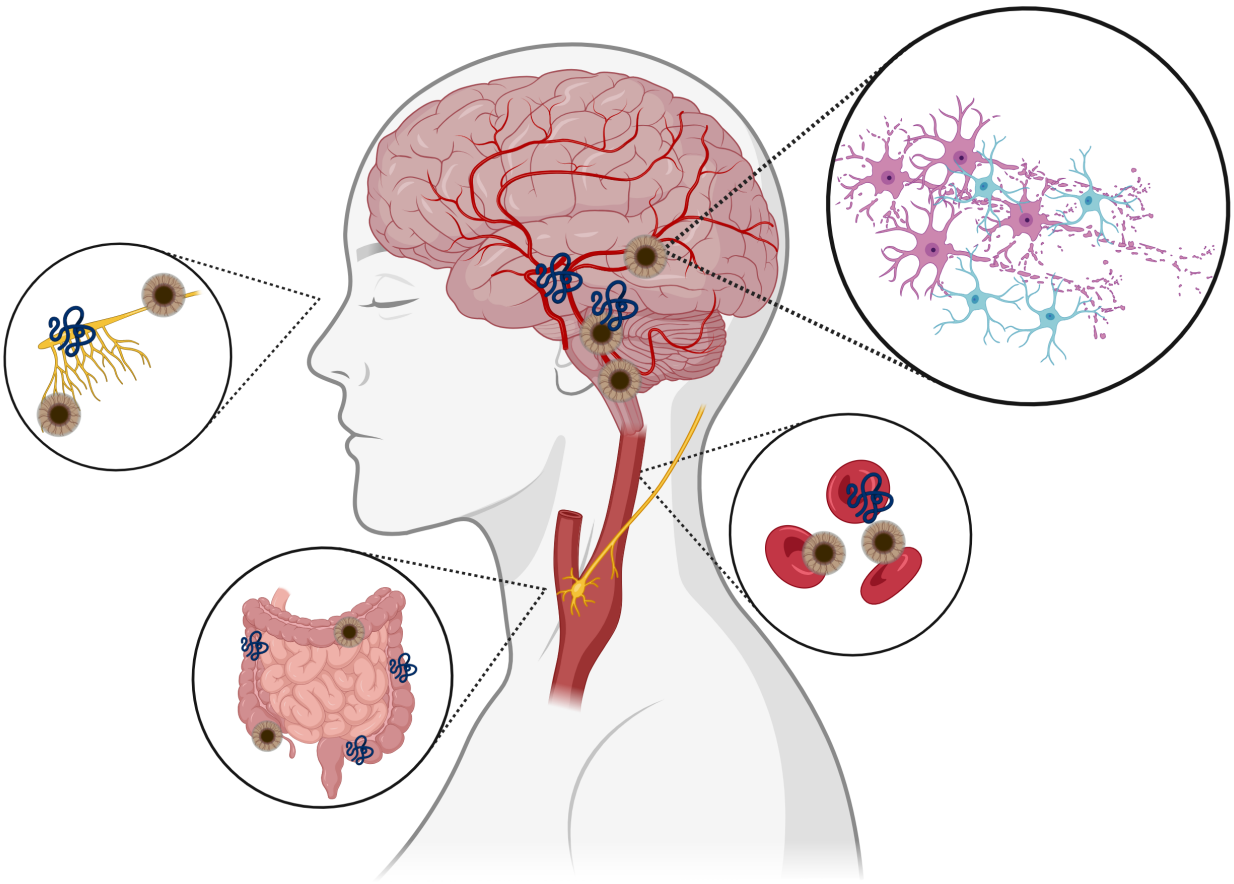

Fig. 2. Hypothesized sources of α-synuclein fibrils and aggregates. Depiction of possible tissue sources that contribute fibrils and aggregates of α-syn to pathophysiology of Parkinson's Disease including the brain, the olfactory bulbs, blood cells, and peripherally via the vagus nerve from enteric neural cells. Created with BioRender.com.

extensively involved [18,58]. As a result, physical translocation of α-syn aggregates from the body to the CNS, where further pathology results in full NDD, is considered the overarching mechanism.

One additional potential pathway within this category is the body fluid circulation pathway, which is also connected to the ANS-associated organs described in gut-first hypotheses. In this pathway, α-syn has been found in many types of circulating fluids, including but not limited to blood, lymph, and cerebrospinal fluid [40]. Indeed, available data has described the types of hematopoietic cells for which α-syn is necessary, and its ubiquitousness in this system is possibly both necessary for homeostasis and yet another method of NDD perpetuation. For example, one mode of transport to the CNS may be through α-syn-laden vesicles derived from erythrocytes, or even α-syn aggregates within RBCs themselves that may appear years prior to frank disease [2,60,62]. Combined with the growing knowledge of α-syn's vital role in the hematopoietic system, such potential sources of aggregates present a rich area for further research. These results serve to strengthen the hypothesis that synucleinopathies may not be the result of one single mechanism or system, no matter the strength of the system's ability to produce aggregates, but rather multiple systems working in tandem—especially with increasing age (Fig. 3).

4. Proposed Treatments for Synucleinopathies

Given the multiple proposed pathways for synucleinopathies and resultant NDD, much attention has been paid to mechanism-specific potential treatments. Due to the dearth of disease attributed to synucleinopathy in extra-neural tissues, the vast majority of effort devoted to synucleinopathy-related disease has been in PD, and discussion of therapeutics past the preclinical stage need be seen through the lens of this disease. An annual review of the currently active clinical trials for PD [63], showed that most small molecules and antibodies have been targeting the dopaminergic pathway per historical reasons. However, other therapeutic strategies, such as targeting gut microbiota, reactive oxygen species (ROS), and immune modulation have also been considered. Here we consider the broadly generalizable findings of such studies with regards to non-CNS mechanisms.

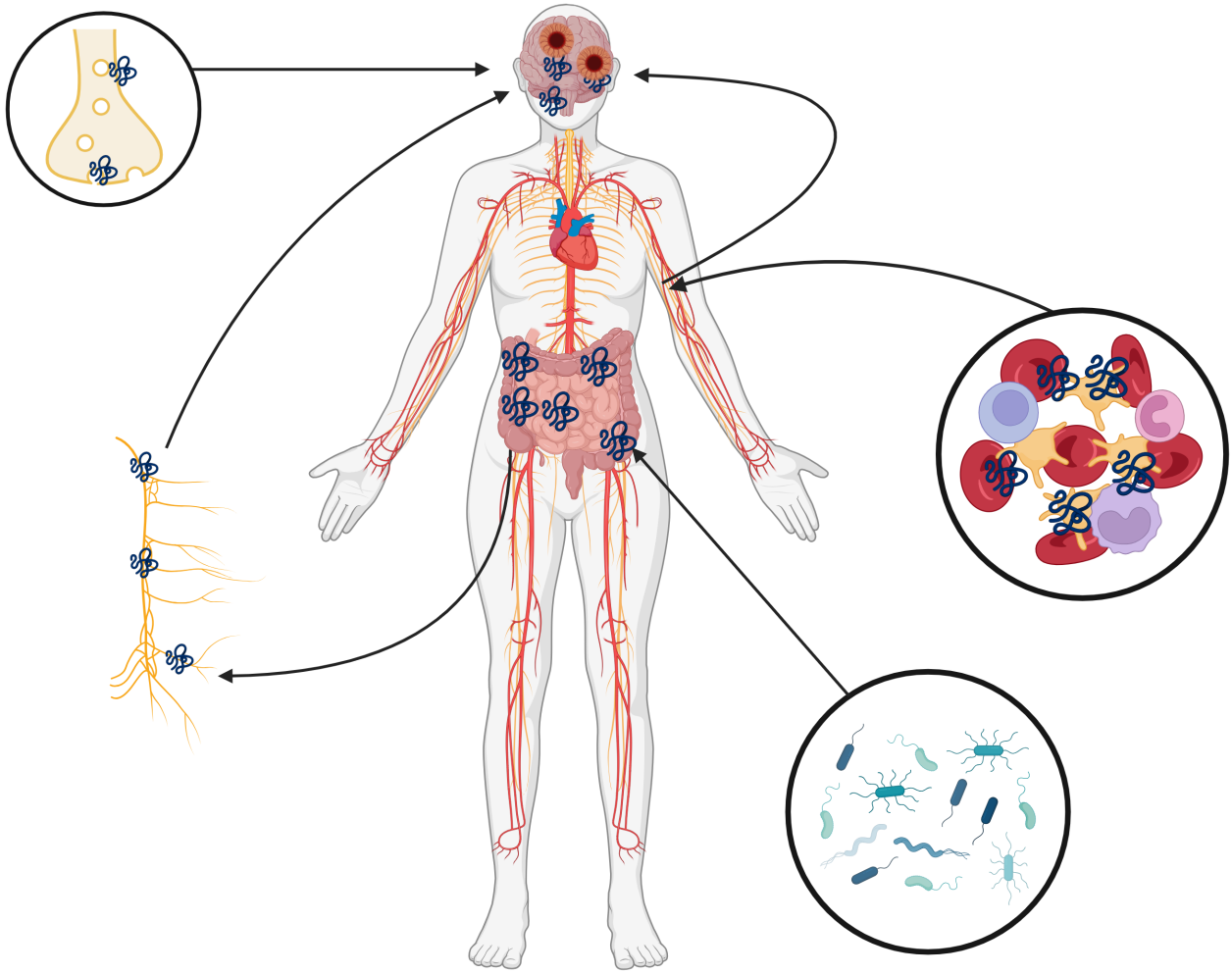

Fig. 3. Potential systemic pathways of synucleinopathies. Stepwise routes of alpha-synuclein aggregation and transport within the gut, hematopoietic system, and central nervous system that may contribute to development of pathology. Created with BioRender.com.

While focus on symptomatic relief through dopaminergic and other pathways comprise a majority of these trials and will not be discussed, a substantial subset targets α-syn directly, with a multitude of completed clinical trials (largely but not exclusively phase I) in recent years. Several general strategies can be identified within this group. The experimental compounds UCB0599 and anle138b have been shown to inhibit α-syn misfolding and oligomerization, respectively; the former has been tested in humans, including PD patients, with a good safety profile. The latter study additionally shows potential action against prion disease, as confirmed by histopathology and decreased signs and symptoms in mice [64,65]. Similarly, the monoclonal antibody prasinezumab, which is specific to α-syn aggregates, is the focus of an ongoing trial [66]. Generalized translation inhibition with the compound buntanetap shows promising results, with additional regulatory effects on neurotoxic proteins in general [67]. Active immunization to α-syn shows sustained aggregate-specific IgG antibody responses (up to one year) against synucleinopathy-specific α-syn epitopes, although the sample size is small [68]. Lastly, non-neurologic drugs such as the diabetes drug lixisenatide have been tested in PD patients [69].

It should be noted that careful review of secondary endpoints and supplementary data of some of these studies demonstrate that actual measurement of α-syn is not generally undertaken [66,69]. The prasinezumab study additionally excludes patients with potential genetic causes of PD, which despite PD's typical occurrence *de novo*, may skew results [66]. Thus, any adverse events that occurred that may be due to secondary effects on extra-neural regions are difficult to account for. Specifically, almost all patients who received the glucagon-like peptide-1 agonist lixisenatide experienced gastrointestinal symptoms; if a pancreatic or ENS effect were the root cause of these symptoms, more caution would need to be exercised in further investigating this specific treatment strategy [69]. Subanalysis of supplementary data in these studies or revisiting biobanks for these clinical trials in the future may be necessary to elucidate the effects of α-syn-targeted therapies on systemic concentrations of the protein.

Separately from the mainstay of targeting α-syn, modulation of the immune system has had ever increasing attention in the synucleinopathy field, particular in Parkinson's disease. As suggested above, the interaction of the hematopoietic compartment, and specifically of the immunity contingent, with synucleinopathies is two-fold. First, treatment that alters α-syn levels may affect normal hematopoiesis, which is dependent partially on normal α-syn concentrations. Second, exaggerated responses in immune cells, particularly microglia [18,42,46], likely contributes to pathogenesis in PD and other NDD. With these factors in mind, the current immunomodulatory therapies available for synucleinopathies can be divided into immune-dampening agents and immune-stimulating factors. The former include the well-studied drugs pentoxifylline and celocoxib as well as more experimental drugs targeting TLR2 and the NLRP3 inflammasome [70–73]. Both TLR2 and the NLRP3 inflammasome complex play important roles in inflammatory signaling and cytokine release, although NLRP3 inhibitors have been studied largely in the context of ulcerative colitis rather than synucleinopathies [72,73]. Nevertheless, inflammatory bowel disease and PD have been linked closely in recent studies, implying the utility of connecting studies based on the former to mechanisms of the latter [61,73]. Conversely, two extended-release GM-CSF compounds have undergone initial testing for use in PD, which suggests a more complex role of inflammation in NDDs than previously thought [74,75].

Paradoxically, the fact that these seemingly opposing agents are being tested for ostensibly the same synucleinopathy-driven pathology suggests a broadly immunological approach may not be the most efficacious choice. On one hand, immune dampening may delay progression or onset of disease while exacerbating disease-related immunosuppression; on the other, attempting to reconstitute decreased immune function may worsen or accelerate pathology. The totality of the effect of the quantitative dysregulation of α-syn, both up and down, should ideally be considered in these broad immunomodulatory approaches, but without further research into the secondary effects of synucleinopathies in the hematopoietic compartment, the non-targeted effects of these approaches may in the end cause more harm than help.

Finally, the gut-brain axis represents a third, major orthogonal approach to studying both the pathogenesis and therapeutic milieu in synucleinopathies [52]. Gut dysfunction, such as through small intestinal bacterial overgrowth, has long been recognized to be correlated with PD [76]. Although a somewhat indirect mechanism, now it is thought that dysbiosis of the gut microbiome can lead to increased neuroinflammation both by aggregation of α-syn in the gut with subsequent migration through the vagus nerve and by permeabilization of the gut lining and subsequent escalation of systemic and downstream CNS inflammation through cytokine action. Accordingly, several approaches to modify the root cause of this pathway have been taken. The antibiotic rifaximin has been proposed as a potential PD treatment and trialed in rodents [77,78]. Alternatively, organism-specific therapies such as fecal microbiota transplantation are gaining traction, as are modulation of the gut microbiome and immune system [38,79–81]. However, a still missing piece of data has been actual measurement of α-syn in non-CNS compartments. If in fact the "gut first" theory holds true, broad analysis of intermediate steps in pathogenesis will eventually require that some quantitative measure of α-syn be undertaken.

Overall, the many different axes of therapeutic investigation in synucleinopathies have a bright outlook, with the above trajectories as well as others unmentioned, such as the role of reactive oxygen species in perpetuating inflammation following α-syn aggregate formation, bearing fruit in the past decade [82]. Nevertheless, in the context of secondary effects on normal α-syn function in other compartments, especially the hematopoietic lineages, only a small minority of effort thus far has been directed towards understanding how the preferential shunting of α-syn to oligomeric forms causes dysregulation systemically. Further studies and therapies may benefit from addressing the body as interconnected, synergistically functioning systems in terms of α-syn sources and pathophysiology.

5. Conclusion

It should be clear from the data presented that the crosstalk of different systems and likely a multiplicity of pathways requiring α-syn are important to establish not only its functional role, but those physiologic axes that require its tight regulation to function properly. Even though this protein has shown to be of great importance in the CNS, it is readily apparent that its function is wide-reaching and involves many systems some of which may prove to contribute to PD and synucleinopathy pathology. It should also be clear that the formulation of hypothesis to account for potential non-CNS sources of the disease takes into account recent findings and thus opens up additional areas for investigation. Thus, therapies will need to be developed that address the multiple effects of α-syn both under normal conditions and in those instances in which its abnormal configurations drive disease symptomatology.

Abbreviations

ANS, autonomic nervous system; α-syn, alpha-synuclein; CNS, central nervous system; ENS, enteric nervous system; GATA-1, GATA-binding protein 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; LBD, Lewy body dementia; MSA, multisystem atrophy; NDD, neurodegenerative disease; NLRP3, NLR family pyrin domain containing 3; OB, olfactory bulb; PD, Parkinson's disease; RBCs, red blood cells; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein re-

ceptors; TLR2, Toll-like receptor 2; VAMP2, vesicle-associated membrane protein 2.

Author Contributions

HHD and BZ performed the literature search and wrote the manuscript; RWM conceptualized the manuscript, wrote key sections, supervised contributions from co-authors, reviewed references, and performed critical revisions. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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