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Review Article

Therapeutic approaches to target alpha-synuclein pathology

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ABSTRACT

Starting two decades ago with the discoveries of genetic links between alpha-synuclein and Parkinson's disease risk and the identification of aggregated alpha-synuclein as the main protein constituent of Lewy pathology, alpha-synuclein has emerged as the major therapeutic target in Parkinson's disease and related synucleinopathies. Following the suggestion that alpha-synuclein pathology gradually spreads through the nervous system following a stereotypic pattern and the discovery that aggregated forms of alpha-synuclein can propagate pathology from one cell to another, and thereby probably aggravate existing deficits as well as generate additional symptoms, the idea that alpha-synuclein is a viable therapeutic target gained further support. In this review we describe current challenges and possibilities with alpha-synuclein as a therapeutic target. We briefly highlight gaps in the knowledge of the role of alpha-synuclein in disease, and propose that a deeper understanding of the pathobiology of alpha-synuclein can lead to improved therapeutic strategies. We describe several treatment approaches that are currently being tested in advanced animal experiments or already are in clinical trials. We have divided them into approaches that reduce alpha-synuclein production; inhibit alpha-synuclein aggregation inside cells; promote its degradation either inside or outside cells; and reduce its uptake by neighbouring cells following release from already affected neurons. Finally, we briefly discuss challenges related to the clinical testing of alpha-synuclein therapies, for example difficulties in monitoring target engagement and the need for relatively large trials of long duration. We conclude that alpha-synuclein remains one of the most compelling therapeutic targets for Parkinson's disease, and related synucleinopathies, and that the multitude of approaches being tested provides hope for the future.

1. Introduction

Undoubtedly, accumulation of misfolded alpha-synuclein (a-syn) into aggregates has a central place in the pathogenesis of Parkinson's disease (PD) and other related synucleinopathies, such as Dementia with Lewy Bodies (DLB) and multiple system atrophy (MSA). In all three of these disorders, the neuropathology is characterised by a-syn accumulation and aggregation, albeit with different cellular predilections and neuroanatomical distributions (Halliday et al., 2011; McCann et al., 2014). The normal function of a-syn in neurons is not well understood, and it is believed that it plays a role in synaptic transmission, specifically in the recycling of synaptic vesicles (Burré, 2015; Burré et al., 2017). The protein is also highly abundant in red blood cells, but its function there is also unknown (Barbour et al., 2008). Under normal conditions a-syn is bound to the membranes of synaptic vesicles (Logan et al., 2017), and is present in the cytosol as a soluble and natively unfolded monomer (Bendor et al., 2013; Burré, 2015; Burré et al., 2017), and possibly also as a tetramer (Bartels et al., 2011), although the existence of a tetrameric form is debated (Fauvet et al., 2012). During the pathogenic process, a-syn misfolds and forms insoluble protein amyloid fibrils, that are the pathological hallmarks of PD, DLB and MSA (Burré et al., 2017; Lashuel et al., 2013).

As has been detailed in other review articles, genetic evidence supports the notion that a-syn can play a causative role in PD and related disorders. In brief, point mutations and multiplications of the *SNCA* gene lead to PD or neurological disorders with parkinsonian features (Lashuel et al., 2013; Nalls et al., 2014; Wales et al., 2013). Normal aging is also associated with increased cytoplasmic levels of soluble a-syn and decreased levels of markers coupled to dopaminergic function in substantia nigra neuronal cell bodies (Chu and Kordower,

Abbreviations: a-syn, Alpha-synuclein; PD, Parkinson's disease; DLB, Dementia with Lewy bodies; MSA, Multiple system atrophy; CNS, central nervous system; MJFF, Michael J Fox Foundation for Parkinson's Research; HSP, Heat shock proteins; mTOR, mammalian target of rapamycin; NAC, Non-Amyloid Component; CSF, cerebrospinal fluid; GAIM, General Amyloid Interaction Motif; MPC, mitochondrial pyruvate carrier; LAG3, lymphocyte-activation-gene 3; PET, positron emission tomography

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2007). Furthermore, single nucleotide polymorphisms close to the *SNCA* locus are also associated with significantly altered PD risk (Nalls et al., 2014). The fact that increased levels of a-syn (due to gene multiplications, nucleotide polymorphisms or normal aging) are associated with neuropathology and disease, suggests that just decreasing the cellular levels of the protein is a possible approach to therapy, and further below we will discuss this as one possible therapeutic strategy.

While there is little doubt that a-syn plays some role in the pathogenesis of PD and related conditions, the precise role is not fully elucidated. It is beyond the scope of this review to discuss in detail which molecular species of a-syn that are pathogenic and how these initially develop (Burré et al., 2017; Dehay et al., 2015; Lashuel et al., 2013; Oueslati, 2016; Wales et al., 2013). Although we will touch upon this topic briefly in a later section, in this review we instead focus on describing a series of therapeutic approaches that all target a-syn in one way or another. We also want to clarify that this review mostly exemplifies treatments directed at PD, but several of the therapeutic approaches are likely also relevant to other synucleinopathies.

Before describing the different approaches to therapy, we provide a short list of outstanding questions regarding the role of a-syn pathology in neurological diseases, together with relevant references to review articles. This list can be used as a backdrop to the discussion of different therapeutic approaches because the questions are relevant to our understanding of how a-syn pathology might be targeted therapeutically. The seven listed issues regarding the role of a-syn in disease pathogenesis are frequently discussed, and therefore worthy of special mention.

First, it remains controversial how upstream in the pathogenic cascade a-syn aggregation is, and whether other molecular events (e.g. mitochondrial failure, oxidative stress, decline of lysosomal function and inflammation) are required triggers (Burré et al., 2017; Dehay et al., 2015; Lashuel et al., 2013; Oueslati, 2016; Wales et al., 2013; Wong and Krainc, 2017). Can a-syn aggregation develop in in otherwise healthy cells, or is failure in energy metabolism, protein homeostasis, antioxidant defences etc. necessary for disease to occur? In some patients (especially those with known mutations in proteins involved in mitochondrial health), is the misfolding of a-syn simply a marker of cell stress and not the root cause of the disease? Considering that aging is the greatest risk factor for PD, even normal cellular aging might be considered the “most upstream” event in the pathogenesis. Aged neurons might represent fertile ground for the seeds of a-syn misfolding to take hold, whereas misfolded a-syn can be effectively cleared by well-functioning, proteostatic mechanisms in young, but otherwise equivalent, neurons (Chu and Kordower, 2007; Jin et al., 2016; Wong and Krainc, 2017). Indeed, such failure of proteostatic mechanisms might explain, at least in part, the selective vulnerability of certain neurons that is seen in the diseased brain (George and Brundin, 2017; Kim et al., 2016a, b). This has implications on therapies that target a-syn, because approaches that counteract cellular aging in the brain might therefore be helpful in reducing PD risk.

Second, it is debated whether the a-syn aggregates that are viewed in the microscope as Lewy pathology, either in neuronal cell bodies (Lewy bodies) or neurites (Lewy neurites), or, in the case of MSA inside oligodendroglia, are the primary cause of cell death. Indeed, it has even been suggested that these large a-syn aggregates actually sequester the more harmful conformers of the protein and might be neuroprotective. Therefore, alternatively, smaller oligomeric species have been suggested to be neurotoxic, and it has even been speculated that monomeric a-syn at supraphysiological levels might be a trigger of lethal molecular cascades. Understanding the role of a-syn oligomers versus fibrils is important when considering what form(s) of a-syn the therapies (e.g. small molecules, antibodies) should target (Melki, 2015; Peng et al., 2017; Wang et al., 2016).

Third, recent discoveries in laboratory models have shown that aggregation-prone a-syn species can be released into the extracellular space and be taken up by neighbouring neurons (Brundin et al., 2016; Goedert et al., 2017; Guo and Lee, 2014; Lee et al., 2014). Once inside the new neuron, the a-syn can seed aggregation of endogenous a-syn. Since a-syn aggregates can be transported along the axon between interconnected brain regions, this “prion-like” mechanism can explain, at least in part, why the disease progresses with both additional symptoms and more widespread Lewy pathology appearing in the brain over time. The implications for this discovery are wide-reaching in a therapy context. If extracellular a-syn plays an important role in the propagation of pathology from one brain region to another in patients, it might be possible to therapeutically minimize the release of misfolded a-syn or reduce the uptake of the protein by neighbouring neurons. Indeed, if a-syn accumulation begins in the periphery (outside the brain), then preventing its propagation to the central nervous system (CNS) could theoretically prevent many of the neurological manifestations of the synucleinopathies.

Fourth, it has been suggested that there exist different molecular species of a-syn aggregates, akin to the “strains” of prion protein that cause different clinical forms of prion disease (Bousset et al., 2013; Melki, 2015; Peng et al., 2017). The putative existence of such a-syn strains could, at least partly, explain why some patients develop PD and others DLB, or MSA. This idea assumes that the biophysical characteristics of the different strains make them more prone to preferentially invade certain cell types. As we will discuss briefly below, this in turn would suggest that a therapy that is effective in one of the synucleinopathies by targeting the prevalent strains of a-syn in that particular disease, might not work in other synucleinopathies. It is even conceivable that the a-syn strains differ between individuals with the same clinical diagnosis, or potentially between different brain regions in the same patient. This would require individualised therapies, or even multiple therapies that selectively target different types of strains in the same patient.

Fifth, while it is widely recognised that Lewy pathology does not develop simultaneously in all parts of the nervous system, there is not full agreement on which brain regions are first vulnerable. Evidence suggests that the olfactory bulb, with closely associated olfactory pathways, and the dorsal motor nucleus of the vagus are two areas that among the first to exhibit Lewy pathology (Braak and Del Tredici, 2017; Del Tredici and Braak, 2016; Rey et al., 2016b; Beach et al., 2009). The a-syn pathology that occurs in sites outside the substantia nigra is likely one of the causes of the signs and symptoms that characterise “prodromal” PD, and therefore this pathology is particularly important when considering early therapeutic intervention. This concept means that monitoring non-motor features of prodromal PD (e.g. anosmia, constipation, sleep disorders, depression), could be excellent measures of therapeutic success; although it should be noted that these features in isolation are not specific for PD (Mahlknecht et al., 2015; Poewe et al., 2017; Schrag et al., 2015). Furthermore, reports that at post-mortem examination 10-30% of normal aged individuals exhibit Lewy pathology in the brain without any associated symptoms (the so called Incidental Lewy Body Disease, which could be a forerunner of the clinical disorders) (Iacono et al., 2015), also suggests that therapies which target a-syn will become increasingly important as the average life-span of populations continue to increase worldwide.

Sixth, it is debated what the true relationship is between accumulation of a-syn, neuronal death and neurological deficits. Some argue that the correlation between Lewy bodies and neuronal death in the afflicted brain regions is poor (Surmeier et al., 2017). It has also been suggested that the accumulation of a-syn in small synaptic aggregates (Lewy neurites) as opposed to the larger Lewy bodies in the soma, are the drivers of neuronal dysfunction and, e.g., cognitive decline (Kramer and Schulz-Schaeffer, 2007). While this is an important consideration, it does not necessarily question the validity of a-syn as a therapeutic target.

Seventh, the role of post-translational modifications of a-syn is not fully understood. In Lewy pathology, some of the a-syn has been cleaved at the C-terminus by calpains (Dufty et al., 2007) while an