Alpha-Klotho in Parkinson’s disease: a perspective on experimental evidence and potential clinical implications

α-Klotho protein (KL) has been discovered more than 20 years ago, and immediately emerged as a master regulator of aging-related processes, which basically operates as an anti-aging factor. It is expressed through the entire human body, representing the choroid plexus and the kidney as the most active sources at the central nervous system (CNS) and periphery level respectively. To a lesser extent, also the parathyroid gland, the adipose tissue, and the liver express KL.

KL is a transmembrane protein serving as an essential co-receptor for fibroblast growth factor receptors, but, in general, it mediates a number of molecular pathways and biological functions at a multisystem level. In fact, even a soluble form exists, originated by the extracellular domain cleavage, which circulates in human fluids, allowing a sort of systemic signaling. Although all the tissue-specific actions have not been completely clarified, there is solid evidence that KL regulates basic mineral homeostasis and internal metabolism pathways. In the CNS, instead, it accounts for wide structural and neuroprotective effects (Cheikhi et al., 2019).

Experimental down-regulation of KL in models causes a premature aging phenotype, including neurodegenerative features, visceral and musculoskeletal involvement, and shorter lifespan. Conversely, the overexpression leads to improved cognition and neuroprotective anti-aging effects; as well, the protein administration prevents and limits damage progression in different models of acute/chronic internal diseases (kidney and heart injuries) via antioxidant and anti-inflammatory mechanisms (Cheikhi et al., 2019).

Several studies linked the higher circulating KL levels to better health outcomes, lower risk for chronic disorders, and longer life expectancy in humans. Contrariwise, the reduction has been associated either with cardiovascular diseases and macrovascular events in patients with type 2 diabetes, or chronic kidney failure complications. Moreover, in many internal, age-related disorders, peripheral KL levels have been correlated with severity of clinical course and prognosis. Accordingly, KL has gained weight as a theoretical biomarker of age-related tissue dysfunction, but also in the context of potential therapies counteracting age-related decline (Cheikhi et al., 2019).

Neurodegenerative diseases, namely Alzheimer’s disease (AD) and Parkinson’s disease (PD) as the two most common forms, dominate the scene of age-related disorders. As expected, the KL pathway is involved even in these conditions. There is evidence that KL is reduced in the brain of AD patients and mouse models; as well, different correlations between KL activity and clinical phenotype or amyloid-β and tau burden have been discovered (Bellou et al., 2020). Regarding PD, instead, first data are just arriving, but they were immediately impressed for the potential clinical implications.

In this perspective, therefore, we will summarize the current evidence on the role of KL in PD, referring to main preclinical and clinical studies; then, we will anticipate the possible next advancements to make KL either a useful biomarker or a candidate therapeutic target for PD.

Involvement of KL pathway in PD and potential clinical implications: PD is a neurodegenerative disorder whose pathological hallmarks are the loss of dopaminergic cells from the substantia nigra pars compacta and the intraneuronal accumulation of α-synuclein positive Lewy bodies. Patients with PD suffer with a progressive, disabling, and heterogeneous syndrome, including the cardinal motor signs (bradykinesia, rigidity, tremor, postural and gait disturbances) and a wide spectrum of non-motor symptoms. Available therapies for PD are based on dopamine replacement, providing only symptomatic relief. Effective disease-modifying treatments, indeed, still lack, as well as reliable disease biomarkers supporting diagnosis, prognostic evaluation, and progression monitoring. The discovery of biomarkers and the development of novel therapies both depend on a deeper comprehension of pathogenic mechanisms of PD. Specifically, there is a need to identify molecules, whose quantitative assessment in peripheral tissues and fluids may inform on the underlying pathological events, but that could also serve as targets for intervention counteracting neurodegeneration and disease progression (Sancesario et al., 2021).

In the last decade, studies from preclinical models and human patients on the involvement of KL in PD supported the research in this field, highlighting a clinical potential for KL pathway in PD field. Experiments on animal models demonstrated the neuroprotective properties of KL in PD, mostly operated via the mitigation of neuropathological changes, the halting of main pathogenic drivers (oxidative stress and neuroinflammation), and the modulation of synaptic plasticity (Cheikhi et al., 2019). Specifically, Kosakai et al. (2011) found that KL-deficient mice, compared to wild-type littermates, had a significant reduction of mesencephalic dopaminergic neurons from both substantia nigra pars compacta and ventral tegmental area, together with lower levels of striatal dopamine. On the other hand, the acute intraperitoneal injection of KL in a PD mouse model expressing transgenic α-synuclein leads to improved cognitive and motor behavior, and enhanced synaptic plasticity in the hippocampus (Leon et al., 2017). As well, the intracerebroventricular injection of KL in the 6-hydroxydopamine lesioned rat model ameliorated motor deficits and tempered down neuropathology, allowing a lower burden of α-synuclein, malondialdehyde, reactive oxygen species, and glial fibrillary acid protein accumulation, together with milder neurodegenerative features (Baluchnejadmojarad et al., 2017).

Recently, clinical data have been also obtained and the shape of KL expression outlined in biofluids of PD patients. Sancesario et al. (2021) provided a paired measurement of KL in cerebrospinal fluid (CSF) and serum of a PD cohort, finding opposite levels in the two compartments. Namely, KL levels were higher than sex-age-matched healthy controls in CSF, and lower in the blood. No correlations resulted between the two pools or with blood-brain-barrier dysfunction, disclosing a distinct KL expression at central and peripheral level, which underlies different pathophysiological mechanisms. In fact, in the CSF, levels of KL and those of total α-synuclein were inversely associated, suggesting that increased expression of KL in the CNS may be a defensive response to the deposition of Lewy bodies. Reduction in the blood, instead, has been considered a consequence of systemic inflammation and oxidative stress, two PD-related phenomena that are able to suppress peripheral expression of KL, as described in other chronic-degenerative diseases. Findings from Sancesario et al. (2021) came from a PD cohort at early disease’s stages (age 59 ± 11 years, disease duration 3.5 ± 3.9 years), when, in theory, defensive responses may be more effective, as the CSF increase of KL in association with accumulating synucleinopathy actually indicates.

In a larger and more clinically-advanced PD cohort, instead, Zimmermann et al. (2021) found that the CSF KL levels were reduced compared to healthy controls and decreased in parallel with worsening of motor disturbances. As well, in a group of patients older than those in Sancesario’s cohort, KL plasma levels, measured by an immunoprecipitation-immunoblotting assay, were similar to healthy controls (Kakar et al., 2021). Despite the limitations due to various assay techniques and different studies
sample sizes, the potential value of KL as a biomarker for PD actually emerged.

In fact, in the CNS, KL expression seems to change depending on disease stage or clinical features overall. In early phases, we may see a compensatory increase, which probably serves to counteract growing neurodegeneration (Sancesario et al., 2021). Consistently, PD patients with KL-VS haplotype, which have a lesser functioning KL protein, develop an aggressive phenotype, with more severe motor impairment and earlier cognitive decline (Zimmermann et al., 2021). Along with PD progression, compensatory mechanisms fail and both neurodegeneration and neuroinflammation spread (Sancesario et al., 2021), with a subsequent inhibition of CNS KL expression and a parallel decline of clinical conditions. CSF KL levels may thus inform on the potentiality of neuroprotective systems of the brain, which is critical to stratify patients especially at the beginning of the disease, and, eventually, to tailor treatments. In the periphery, instead, KL is mostly produced by the kidney and a reduction of circulating levels has been measured in patients with kidney disorders, diabetes, and chronic-degenerative diseases, often with high predictive value in clinical terms (Sancesario et al., 2021). Similarly, in PD, the blood KL levels may serve as a systemic readout of critical pathogenic processes, such as oxidative stress and inflammation, which could be extremely useful to better characterize the individual biological profile of each patient (Figure 1).

More recently it has raised the hypothesis that, in some cases, PD-pathology may start from the enteric or the peripheral autonomic nervous system, and successively ascend to CNS mostly via the vagus nerve (“body-first hypothesis”) (Horsager et al., 2020). Actually, gut inflammation has a major role in PD pathogenesis or progression, and may also precede the overt phases of the disease (Brudik, 2019). Of interest, systemic levels of KL decrease in the presence of intestinal inflammation and bowel inflammatory diseases (Thurston et al., 2010), thus supporting the idea that circulating KL basically reflects events occurring out from the CNS, but definitely linked to PD mechanisms. The enteric cells, especially in the colon, also express KL. The abnormal intestinal expression of KL has been then associated with local diseases; namely, a recent study showed that colorectal cancer cells present lower KL levels compared to normal tissue. Conversely, KL overexpression or the external administration inhibit cancer proliferation (Arbel Rubinstein et al., 2019).

Actually, these data laid the foundations for a direct assessment of KL into the gastrointestinal tract of PD patients for clinical purposes. Besides the direct detection of KL in the enteric mucosa, gastrointestinal KL might be better evaluated in more easy accessible sites, such as the mouth. In fact, KL is expressed by oral mucosa and salivary glands (Tai et al., 2019), which already represent useful sources for fluid biomarkers in PD (Bougea et al., 2019). Likewise, the modulation of KL levels into the gut rises as a novel, hypothetic, disease-modifying treatment for PD, targeting one of the earliest sites of neuropathology.

Conclusions: In conclusion, we have initial evidence that expression of KL could dynamically reflect either at a central or systemic level the critical molecular mechanisms underlying the various phases of PD. Measurement of KL in different tissues (CSF, blood, other peripheral tissues) might thus inform on the burden of pathogenic forces and the presence of some compensatory attempts, which is fundamental to identify the ideal time-window for successful therapeutic interventions. Moreover, there are encouraging data indicating KL as a valuable candidate target for novel therapies in PD field.

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