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Role of PARK7/DJ-1 in Gastrointestinal Diseases

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Abstract Parkinson's disease 7 (PARK7/DJ-1) is an evolutionarily conserved multifunctional protein whose role has been widely demonstrated in malignant tumours and neurodegenerative diseases, including Parkinson's or Alzheimer's disease. However, recent studies also revealed protective role of PARK7/DJ-1 regarding gastrointestinal diseases. In the present review, we discuss our current knowledge about PARK7/DJ-1 in the context of coeliac and inflammatory bowel disease.

Keywords: *PARK7/DJ-1, coeliac disease, inflammatory bowel disease,Crohn's disease, ulcerative colitis*

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1. Introduction

PARK7/DJ-1 is a conservative homodimer, which is present in most of the human cells [1]. Previous studies suggest that oxidative stress is the main determinant of the amount and activity of PARK7 [2]. However, recent data support that mechanisms, regulating the synthesis and stability of PARK7/DJ-1 are more complex (Table 1) [3].

Based on the literature, PARK7/DJ-1 can interact with more than 300 proteins and genes [4]. Although the biological significance of these interactions has not been fully explored, the high number of interactions suggests the wide-range biological effects of PARK7/DJ-1.

Perhaps the most well-known function of PARK7/DJ-1 is the protection of cells against oxidative stress. It has been observed that a loss-of-function mutation of PARK7/DJ-1 reduces the resistance of neurons to oxidative stress, leading to the early onset of neurodegenerative diseases such as juvenile Parkinson's disease [5,6].

PARK7/DJ-1 protects the cells against oxidative stress through various pathways. PARK7/DJ-1, as a peroxiredoxin-like peroxidase, is able to eliminate the intracellular reactive oxygen species (ROS) through the oxidation of its Cys106 (Cysteine-106) [18]. Also, in response to oxidative stress PARK7/DJ-1 translocates into the mitochondria where it can enhance the activity of NADH dehydrogenase to inhibit oxidative stress [19,20,21,22,23,24].

Table 1. Regulation of PARK7/DJ-1

Molecule	Effect on PARK7/DJ-1	Investigated sample	References
Negative regulators of PARK7/DJ-1			
H_2O_2	Excessive oxidation of PARK7/DJ-1	human brain	[2,7]
BAG5	Decreased stability of PARK7/DJ-1	HEK293 human embryonic kidney cell	[8]
LPS	Decreased synthesis of PARK7/DJ-1	HT-29 human colorectal adenocarcinoma	[9]
miR-128-3p	Decreased expression of PARK7/DJ-1	Human hepatocellular carcinoma	[10]
miR-203	Decreased expression of PARK7/DJ-1	Human pancreatic adenocarcinoma	[11]
miR-494	Decreased expression of PARK7/DJ-1	Mouse adipocytes and neuroblastoma	[12]
MMP-3	Fragmentation of PARK7/DJ-1	CATH.a mouse neuron	[13]
p53	Decreased expression of PARK7/DJ-1	mouse embryonic fibroblasts	[14]
TGF-β	Decreased synthesis of PARK7/DJ-1	HT-29 human colorectal adenocarcinoma	[9]
TNF-α	Decreased synthesis of PARK7/DJ-1	HT-29 human colorectal adenocarcinoma	[9]
miR-4639-5p	Decreased expression of PARK7/DJ-1	HEK-293T	[15]
Positive regulators of PARK7/DJ-1			
H_2O_2	Increased synthesis of PARK7/DJ-1	HT-29 human colorectal adenocarcinoma	[9]
IL-17	Increased synthesis of PARK7/DJ-1	HT-29 human colorectal adenocarcinoma	[9]
STAT5A	Increased expression of PARK7/DJ-1	Human leukemia pre-B cell	[16]
SG2NA	Increased stability of PARK7/DJ-1	Neuro2a neuroblastoma	[17]

However, the most important antioxidant function of PARK7/DJ-1 is the activation of the nuclear factor erythroid 2–related factor 2 (NRF2), which plays a determinative role in the antioxidant defence by regulating the expression of several antioxidant genes, including thioredoxin (TRX1), glutamate-cysteine ligase catalytic subunit (GCLC), heme oxygenase-1 (HMOX1), and NAD(P)H quinone dehydrogenase-1 (NQO1) [25,26].

In addition to its direct antioxidant effects, PARK7/DJ-1 helps to eliminate the toxic metabolites of glucose in the body. During the Maillard reaction glucose degradation products (GDP) are produced from glucose. GDPs react with various macromolecules to create advanced glycation end products (AGE) [27]. AGEs play a role in the pathomechanism of many diseases, including diabetes mellitus, inflammatory bowel disease (IBD), Alzheimer's or Parkinson's disease via protein cross-linking and oxidation of nucleic acids and lipids [28,29,30]. Besides, AGE-modified molecules bind to many cell surface receptors, including their receptors (RAGE), and are linked to multiple inflammation-related pathologies via NF-κB signaling [31].

PARK7/DJ-1 intervenes in the degradation of the toxic GDPs and AGEs at several points. By increasing the synthesis of glutathione, the cofactor of glyoxalase-I and -II, PARK7/DJ-1 contributes to the degradation of harmful GDPs (Figure 1.) [32,33,34]. During the enzymatic process, GDPs are broken down into pyruvate through lactoyl glutathione and lactate. In addition to its effect on glutathione synthesis, PARK7/DJ-1 also has endogenous glyoxalase and deglycase activity, which contribute to the breakdown of GDP and the restoration of glycated molecules [32,35].

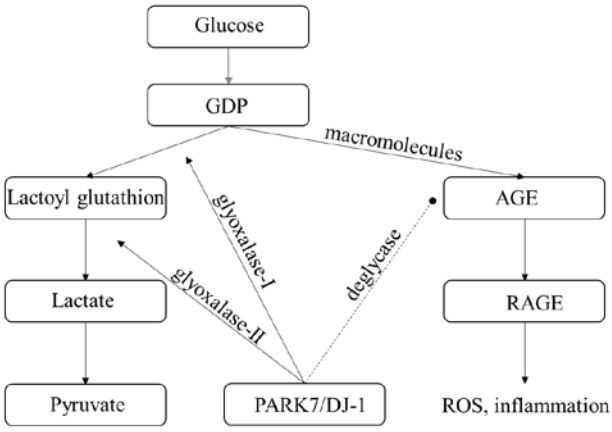

Figure 1. Effects of PARK7/DJ-1 on the formation and degradation of AGEs [3]

2. Role of PARK7/DJ-1 in the Development of Gastrointestinal Diseases

PARK7/DJ-1 was first described as an oncogene, accordingly its increased expression was demonstrated in many tumours, including glioblastoma, non-small cell lung cancer, thyroid, breast, pancreatic, hepatocellular, and gastrointestinal carcinomas [36,37,38]. Later the decreased function of PARK7/DJ-1 was linked with neurodegenerative diseases like Parkinson's, or Alzheimer's disease and also with diseases of the heart or lung [3,39,40].

The possible role of PARK7/DJ-1 in the pathomechanism of coeliac disease was first suggested by a genome-wide association study of Dubois et al. and a year later a similar association of PARK7/DJ-1 and ulcerative colitis (UC) was suggested by Anderson et al. [41,42]. Thereafter, our findings demonstrated the protective role of PARK7/DJ-1 in IBD, and in coeliac diseases, as well [9,43]. Finally, recent results of Singh et al. suggested that PARK7/DJ-1 helps to maintain the homeostasis of the gut [44].

2.1. Role of PARK7/DJ-1 in Coeliac Disease

Further human evidence about the role of PARK7/DJ-1 in gastrointestinal diseases was the study of Vörös et al. [45]. In this study, our group demonstrated the increased presence of PARK7/DJ-1 in the duodenal epithelial and lamina propria cells of pediatric patients with untreated coeliac disease. Interestingly the amount of PARK7/DJ-1 in the duodenal biopsies of coeliac children on gluten-free diet was similar to that of control children, suggesting the role of PARK7/DJ-1 in the pathomechanism of coeliac disease [45]. Therefore, the possible role of PARK7/DJ-1 was further investigated in in vitro and ex vivo experiments. We found that Comp23 (CAS No. 724737-74-0), a compound that protects Cys106 of PARK7/DJ-1 from excessive oxidation, decreased the accumulation of ROS in H_2O_2 treated duodenal epithelial cells. The beneficial effect of Comp23 was related to its effect on the expression of NRF2, the major regulator of antioxidant defence, and NRF2 regulated genes including TRX1, GCLC, HMOX1, and NQO1 [43]. These observations were in line with previous experiments demonstrating that lack of PARK7/DJ-1 is associated with increased presence of ROS [46,47]. Comp23 treatment also restored the expression of cell adhesion molecules of duodenal epithelial cells, including zonula occludens 1 (ZO-1), cadherin 1 (CDH1), vinculin (VCL), and integrin subunit beta 5 (ITGB5), reduced by oxidative stress. Not surprisingly the survival of Comp23 treated duodenal epithelial cells was improved during oxidative stress. Overall, all these beneficial effects of Comp23 led to decreased permeability of small intestinal sacs ex vivo, suggesting the role of PARK7/DJ-1 in the maintenance of intestinal integrity [43].

2.2. Role of PARK7/DJ-1 in Inflammatory Bowel Disease

Our knowledge about the possible role of PARK7/DJ-1 in the pathomechanism of IBD is restricted to only a few studies. Previously, Narzo et al. investigating the plasma proteome of adult patients with Crohn’s disease (CD) and UC demonstrated that the amount of 493 proteins changed compared to that of healthy subjects. Among them, the amount of PARK7/DJ-1 was increased in the plasma of UC patients compared to that of healthy subjects [48]. On the contrary, Zhang et al. found decreased levels of PARK7/DJ-1 in the intestine of patients with active CD or UC compared to healthy subjects [49]. Finally, our

research group demonstrated increased amount of PARK7/DJ-1 in the macroscopically inflamed and also in the non-inflamed mucosa of therapy naive children with CD [9]. However, according to our observation, the amount of PARK7/DJ-1 was unchanged in the mucosa of children with UC. An obvious explanation for the contradictions may be that the above mentioned studies examined very different human samples. Indeed, while Narzo et al. investigated the plasma samples of adults, and Zhang et al. paraffin-embedded histological samples, our group investigated the fresh frozen intestinal biopsies of therapy naive children with IBD.

According to the observations on experimental animals Zhang et al. demonstrated that following DSS treatment more severe symptoms develop in the PARK7/DJ-1 gene knockout (KO) mice than in the wild type ones [49]. Similarly, we revealed that the disease activity index is less pronounced in the Comp23 treated mice with DSS induced colitis compared to DSS treated mice [9].

These experiments also showed that the PARK7/DJ-1 has an impact on the inflammation of the colon of DSS treated mice. Indeed, in line with the clinical symptoms, the presence of active PARK7/DJ-1 inhibited the expression of several proinflammatory factors, including interleukin (IL)-1β, IL-6, IL-8, IL-10, transforming growth factor-beta (TGF-β), monocyte chemotactic protein-1 (MCP1) or C-C motif chemokine 3 (CCL3) in the colon of mice with DSS induced colitis [49].

Table 2. PARK7/DJ-1 regulated proinflammatory cytokines

	DSS treated PARK7 /DJ-1-/- mice	Comp23 and DSS treated wild type mice
IL-1β	increased	decreased
IL-6	increased	decreased
IL-8	increased	not investigated
IL-10	not investigated	decreased
TGFβ	not investigated	decreased
MCP1	increased	not investigated
CCL3	increased	not investigated

To further clarify the role of PARK7/DJ-1 Zhang et al. generated bone marrow chimera mice. When PARK7/DJ-1 was disrupted only in the myeloid cells of otherwise wild type mice the clinical symptoms of DSS treated mice were less pronounced, and the expression of IL-1β, IL-6, MCP1, or CCL3 was decreased compared to that of wild type mice. When, on the contrary, only the myeloid cells of the PARK7/DJ-1KO mice expressed PARK7/DJ-1 the colitis was more severe and the expression of IL-1β, IL-6, MCP1 or CCL3 was increased in the colon. Taken together, Zhang et al. suggested that while the presence of PARK7/DJ-1 in the colon epithelial cells may have beneficial effects on the clinical symptoms of DSS induced colitis its presence in the myeloid cells can worsen the outcome of the disease [49].

All these data suggest that PARK7/DJ-1 plays a determinative protective role in the pathomechanism of coeliac and inflammatory bowel diseases. Moreover, Comp23 as a low molecular weight compound can reduce both the oxidative stress and inflammation in the in vitro and also in the in vivo models of gastrointestinal diseases, suggesting that PARK7/DJ-1 is a possible target of later drug development.

2.3. Role of PARK7/DJ-1 in Microbiome and Metabolome Homeostasis

Recent study of Singh et al. investigated whether lack of PARK7/DJ-1 affects the intestinal microbiota composition and metabolite production [44]. They compared the bacterial composition of the feces of wild type and PARK/DJ-1 KO mice by 16S rRNA sequencing. Their data showed that although the overall composition of the feces microbiome did not differ between the wild type and PARK7/DJ-1 KO mice, the ratio of Firmicutes and Bacteroidetes - the two largest bacterial phyla making up the gut microbiome - was changed [50]. Indeed, the amount of IBD related species Alistipes and Rikenella was increased in PARK7/DJ-1 KO mice [51]. Changes in the composition of the intestinal microbiome can affect its metabolite production. Accordingly, they demonstrated that the amount of fecal and serum amino acids and short-chain fatty acids were altered in PARK7/DJ-1 KO mice, which can lead to metabolic stress. Besides, they found increased levels of proinflammatory MCP-1 and calprotectin in the feces of PARK7/DJ-1 KO mice. Their results suggest the importance of PARK7/DJ-1 in the maintenance of gut homeostasis, and also that its decreased expression or absence can induce pathologic alterations.

3. Conclusion

It is known that PARK7/DJ-1 interacts with many molecules which may affect the processes of oxidative stress and inflammation, as well. Although the literature data are somewhat contradictory, overall it suggests that PARK7/DJ-1 plays a determinative protective role in the pathomechanism of coeliac and inflammatory bowel diseases. Moreover, Comp23 as a low molecular weight compound can reduce both the oxidative stress and inflammation in the gut, suggesting that PARK7/DJ-1 is a possible therapeutic target in the treatment of gastrointestinal diseases.

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