Blood and CSF Biomarkers in Autosomal Dominant Cerebellar Ataxias

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Abstract A biomarker can be defined as a measurable indicator of the presence or severity of a disease state, often present before clinical signs are evident. For the most frequent forms of spinocerebellar ataxia (SCAs), due to expansions of coding CAG repeats SCA1/*ATXN1*, SCA2/*ATXN2*, SCA3/*ATXN3*, SCA6/*CACNA1A*, SCA7/*ATXN7*, SCA17/*TBP,* and DRPLA/*ATN1,* gene therapies are planned. Reliable biomarkers should indicate the pathological onset or discriminate disease stages that would allow to stratify patients and to monitor drug efficacy. This chapter reviews the available blood and cerebrospinal fluid (CSF) biomarkers. One of the most promising biomarkers is neurofilament light chain (NfL) for which blood and CSF levels accurately correlate. Moreover, NfL concentrations are associated with disease progression, and cerebellum and brainstem atrophy. Specific ataxin bioassays are in development for polyglutamine SCAs, but only ataxin-3 can be measured in blood and CSF. Other biomarkers are related to oxidative stress, inflammation, astrogliosis, and insulin pathway. Others are in development regarding the metabolism of cholesterol, lipids, and amino acids, as well as the microRNAs that would be potential biological markers of disease and therapeutic targets.

Keywords Spinocerebellar ataxias · SCAs · Biomarkers · Gene therapy

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1 Introduction

Autosomal dominant cerebellar ataxias (ADCAs) are a rare cause of cerebellar ataxias. In genetic nomenclature, they referred to spinocerebellar ataxias (SCAs), a group of diseases clinically and genetically heterogeneous (Klockgether et al. 2019). Nowadays, 48 SCAs subtypes have been identified. The most frequent SCAs are due to pathological CAG repeat expansions coding for polyglutamine (polyQ): SCA1/*ATXN1*, SCA2/*ATXN2*, SCA3/*ATXN3*, SCA6/*CACNA1A*, SCA7/*ATXN7*, SCA17/*TBP* and DRPLA/*ATN1*. Age at onset and disease severity are negatively correlated with the pathological CAG repeat expansion (Durr 2010), and phenotype is clearly associated with CAG repeat size (Stevanin et al. 2000). Pediatric and juvenile forms can also occur, especially for SCA2 and SCA7 (Mao et al. 2002; Bah et al. 2020). PolyQ subtypes clinically share the cerebellar ataxia with gait and balance impairment, limb dysmetria, dysarthria, swallowing difficulties, and oculomotor abnormalities. However, other extra-cerebellar signs are also present: pyramidal syndrome for SCA1, SCA3, SCA7, SCA17, parkinsonism for SCA2, SCA3, SCA7, fasciculations and wasting for SCA2, peripheral neuropathy for SCA2 and SCA3, dystonia for SCA2, SCA3, SCA7, SCA17, choreic movements for SCA17, ophthalmological deficit for SCA7, etc. The Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al. 2006), which includes eight items to assess cerebellar syndrome, does not catch these extra-cerebellar signs. This scale is used as the primary outcome in several therapeutic and non-therapeutic trials for SCAs. However, presymptomatic carriers, defined by a SARA score <3 out of 40, can present other non-cerebellar signs and symptoms that are already expression of disease.

Individual variability, even among genetically homogeneous forms due to a same mutation, impedes prediction of progression of the imaging and clinical signs in ataxias. Broadly, a higher number of CAG repeats within the *HTT* gene predicts earlier onset, but two people with the same repeat length may differ in clinical onset by decades (Lee et al. 2012). This variability has to be tackled using biomarkers that allow to define the state of disease for a single patient and the challenge for the evaluation of potential treatments, particularly in early stages, will rely on longitudinal biomarkers.

Gene therapies have made remarkable progress over the last decade, such as antisense oligonucleotides (ASOs) approach. These are targeted treatment based on the genetic status. The rationale relies on the fact that lowering the burden of mutated protein may improve the disease prognosis. ASOs form a complex with targeted mRNA recruiting an endoribonuclease (Ribonuclease H) that degrades the RNA-DNA hybrid complex (Wild and Tabrizi 2017). Following the impressive results of nusinersen in spinal muscular atrophy (Finkel et al. 2017; Acsadi et al. 2021), major hopes have been put in the development of ASO directed to *ATXN1*, *ATXN2*, *ATXN3,* and *ATXN7* mutants even though one recent phase-III clinical trial failed to show that ASOs halted the progression of Huntington disease (HD) (Tabrizi et al. 2019; Kingwell 2021). Promising results have been reported by the ASOs administration in several SCAs mouse models (Friedrich et al. 2018; Scoles et al. 2017; McLoughlin et al. 2018; Niu et al. 2018). Therefore, objective and quantitative biomarkers rather

than clinical measures are of critical importance as prognostic or pharmacodynamic markers to monitor drug effects. The aim of this chapter is to review the blood and cerebrospinal fluid (CSF) biomarkers for SCAs (Table 1).

2 Biological Biomarkers

2.1 Neurofilament Light Chain

Neurofilament light chain (NfL) is a subunit of neuronal cytoskeleton and its level increases in CSF and blood as a result of axonal damage due to different causes (neurodegeneration, infection, traumatic, etc.) (Gaetani et al. 2019). Using the highly sensitive single-molecule array method (Simoa) is possible to measure NfL in blood and CSF more accurately than conventional enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence-based method (ECL assay) (Kuhle et al. 2016). Close correlation exists between CSF and blood concentrations, making NfL an easily measurable biomarker of neurodegeneration (Gaetani et al. 2019; Khalil 2018). In several neurological disorders, NfL correlates with disease stages, clinical scores, and neuroimaging data. It is the case for amyotrophic lateral sclerosis (ALS) (Lu et al. 2015; Benatar et al. 2018), Alzheimer's disease (Mattsson et al. 2019; Benedet et al. 2020; Preische et al. 2019), and multiple sclerosis (Bjornevik et al. 2020; Kuhle et al. 2019), HD (Byrne et al. 2017; Johnson et al. 2018; Scahill et al. 2020). This latter disease shares with SCAs the same mutational mechanism, a translated pathological CAG repeat expansion. NfL showed a prognostic value with a significant increase for HD presymptomatic carriers of the pathological expansion close to the age at expected disease onset (Scahill et al. 2020). Moreover, for HD, atrophy of cerebral regions, as the putamen and caudate, is associated with higher NfL concentrations (Scahill et al. 2020).

For SCAs, some studies showed the higher NfL levels in carriers than healthy controls. The first pilot study included only 20 SCAs carriers (SCA1, SCA2, SCA3, SCA6) founding elevated Nfl concentrations compared to controls (Wilke et al. 2018). Then, other studies on large cohorts of SCA3 carriers confirmed the correlation between clinical progression and NfL in CSF (Li et al. 2019) and blood (Li et al. 2019; Wilke et al. 2020; Peng et al. 2020). In a longitudinal study with 2-year interval of plasma NfL measurements, NfL confirmed to be a disease biomarker with significant difference between healthy controls (~10 pg/mL) and polyglutamine (polyQ) SCAs carriers [SCA1 (~24 pg/mL), SCA2 (~20 pg/mL), SCA3 (~35 pg/mL), and SCA7 (~26 pg/mL)] (Coarelli et al. 2021). Interestingly, NfL concentrations remained stable at 2-year follow-up despite clinical progression assessed by SARA (Coarelli et al. 2021). Considering all SCAs subtypes, higher plasma NfL levels at baseline predicted a higher SARA score progression as well as a decrease in cerebellar volume at 2-year follow-up (Coarelli et al. 2021). NfL correlated with pons atrophy at baseline and follow-up (Coarelli et al. 2021), confirmed for SCA3 group taken separately. For SCA3, another study also reported significant

Table 1 Blood and cerebrospinal fluid biomarkers in spinocerebellar ataxias

Mechanism	Biomarker	Results	Correlations
Neuroaxonal damage	NfL	↑ in serum SCA1, SCA2, SCA3, SCA6 (Wilke et al. 2018) ↑ in plasma SCA1, SCA2, SCA3, SCA7 (Coarelli et al. 2021) ↑ in plasma and CSF of pre-symptomatic and symptomatic SCA3 (Li et al. 2019) ↑ in serum of symptomatic SCA3 (Wilke et al. 2020)	For SCA3: disease stage (Li et al. 2019; Wilke et al. 2020), CAG (Wilke et al. 2020), SARA (Li et al. 2019; Wilke et al. 2020; Coarelli et al. 2021), CCFS (Coarelli et al. 2021), pons atrophy (Coarelli et al. 2021), cerebellum and brainstem atrophy (Li et al. 2019) For polyQ SCAs: SARA, CCFS, pons atrophy (Coarelli et al. 2021); disease stage, disease duration, SARA (Shin et al. 2021)
	Phosphorylated neurofilament heavy chain	↑ in serum of SCA3 (Wilke et al. 2020)	
	Tau	↑ in CSF of SCA2 (Brouillette et al. 2015)	No
Astricitosis and gliosis	Neuron-specific enolase	↑ in serum of SCA3 (Zhou et al. 2011)	Disease duration, ICARS, and SARA (Zhou et al. 2011)
	S100B	↑ in serum of SCA3 (Zhou et al. 2011)	No
ATXN-3 bioassays	Expanded polyQ ATXN-3	Detection in PBMC by TR-FRET immunoassay in pre-symptomatic and symptomatic SCA3 (Gonsior et al. 2020)	Disease stage and SARA (Gonsior et al. 2020)
		Detection in plasma and CSF by electrochemiluminescence immunoassay in pre-symptomatic and symptomatic SCA3 (Prudencio et al. 2020)	No
		Detection in plasma and CSF by single molecule counting in pre-symptomatic and symptomatic SCA3 (Hübener-Schmid et al. 2021)	Age at onset (negative correlations) and SARA for plasma ATXN-3 levels (Hübener-Schmid et al. 2021)

(continued)

Table 1 (continued)

Mechanism	Biomarker	Results	Correlations
Oxidative stress	Superoxide dismutase	↓ in serum of symptomatic than in pre-symptomatic SCA3 carriers (de Assis et al. 2017)	No
	Glutathione peroxidase	↓ in serum of symptomatic than in pre-symptomatic SCA3 carriers (de Assis et al. 2017)	Negative correlation with NESSCA (de Assis et al. 2017)
	Catalase	↑ in serum of SCA3 (Pacheco et al. 2013)	No
Inflammation	Eotaxin	↑ in serum of asymptomatic SCA3 carriers (da Silva et al. 2016)	No
Growth factors	IGFBP1 IGF-1/IGFBP-3 ratio	↑ in serum of SCA3 patients (Saute et al. 2011)	CAG repeat expansion (Saute et al. 2011)
	IGFBP-3 Insulin	↓ in serum of SCA3 patients (Saute et al. 2011)	No
Chaperon	CHIP	↑ in serum and CSF of SCA3 patients (Hu et al. 2019)	SARA and ICARS (Hu et al. 2019)
Metabolism	CYP46A1	↓ in SCA3 cerebellum samples (Nóbrega et al. 2019)	No
	Valine, leucine, tryptophan, and tyrosine	↓ in serum of SCA3 patients (Yang et al. 2019)	No
	Leucine, valine, and tyrosine	↓ in serum of SCA7 patients (Nambo-Venegas et al. 2020)	No
	Ceramides and phosphatidylcholines	↓ in plasma of SCA7 patients (Garali et al. 2018)	No
Enzyme	Sirtuin-1	↓ mRNA in SCA3 patients' fibroblasts (Cunha-Santos et al. 2016)	No
Micro-RNAs	miR-25, miR-125b, miR-29a, and miR-34b	↓ in serum of SCA3 patients (Huang et al. 2014; Shi et al. 2014)	No
	hsa-let-7a-5p, hsa-let7e-5p, hsa-miR-18a-5p, and hsa-miR-30b-5p	Alterations in plasma of SCA7 patients (Borgonio-Cuadra et al. 2019)	Disease onset (Borgonio-Cuadra et al. 2019)

Abbreviations: *CCFS* Composite Cerebellar Functional Score, *CHIP* carboxyl terminus of the Hsp70-interacting protein, *ICARS* International Cooperative Ataxia Rating Scale, *IGFBP* insulin-like growth factor-binding protein, *NfL* neurofilament light chain, *polyQ* polyglutamine, *S100B* protein S 100 B, *SARA* Scale for the Assessment and Rating of Ataxia, *SCA* spinocerebellar ataxia

association between serum NfL and cerebellum and brainstem volumes (Li et al. 2019).

Serum NfL increases already 7.5 years before the expected age at onset for SCA3 carriers (Wilke et al. 2020). NfL levels for SCA3 presymptomatic carriers fall down

between controls and symptomatic carriers levels (Li et al. 2019; Wilke et al. 2020; Peng et al. 2020; Coarelli et al. 2021). SCA7 premanifest carriers with non-cerebellar signs at examination present NfL concentration close or above the cut-off level determined to differentiate controls from carriers (Coarelli et al. 2021). Based on presymptomatic carriers' data (Li et al. 2019; Wilke et al. 2020) and longitudinal data (Coarelli et al. 2021), NfL seems to be a biomarkers that may be used in clinical trials to stratify carriers based on their NfL levels. However, some points remain to be clarified: (i) SCA3 patients present the highest concentration than the other SCAs despite a less severe clinical progression based on SARA score (Coarelli et al. 2021; Jacobi et al. 2015). One possible explanation may be the prominent peripheral nervous system involvement than the other polyQ SCAs; (ii) NfL levels do not change over time in SCAs, similar to ALS, frontotemporal dementia, and atypical parkinsonian syndromes (Gaetani et al. 2019). We may suppose that for these diseases NfL levels reach a plateau that masks the increase due to age. (iii) NfL concentrations for polyQ SCAs fall between the highest levels of ALS or multiple system atrophy and the lowest levels in Friedreich's ataxia or Parkinson disease (Gaetani et al. 2019; Bridel et al. 2019). It may be due to by either different disease progression rates or different levels of peripheral nervous system dysfunction.

2.2 Tau

Another biomarker of neuroaxonal damage is Tau protein that promotes microtubule assembly and stability. This protein is an established marker in Creutzfeldt Jakob disease and Alzheimer's disease (Tumani et al. 2008). In a study including few SCA1, SCA2, and SCA6 patients, Tau levels in CSF were significantly higher in SCA2 carriers than controls (Brouillette et al. 2015). Other proteins were also tested in CSF (α-synuclein, DJ-1, and GFAP) showing a tendency to be higher especially for SCA2 (Brouillette et al. 2015) and indicating the necessity to be reproduced in a larger cohort of patients.

2.3 Astrocytosis and Gliosis

Neuron-specific enolase (NSE) and protein S 100 B (S100B) are markers of neuron damage and gliosis. Serum concentrations of these two proteins are higher in SCA3 patients than controls (Zhou et al. 2011), not tested in other SCA patients. NSE presents a correlations with disease duration and clinical scales (ICARS and SARA), instead of S100B that does not correlate with any clinical parameters (Zhou et al. 2011). In another SCA3 study, only NSE serum level was significantly higher than controls and presented a correlation with depression score (Tort et al. 2005).

2.4 Ataxin-Specific Bioassays

In view of upcoming therapeutic trials that aim to decrease the mutant protein, it seems to be crucial for the development of ataxin-specific assays to monitor the efficacy of these treatments. To date, a time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassay can detect the polyQ-expanded and non-expanded ataxin-3 protein level in blood-derived mononuclear cells from presymptomatic and symptomatic SCA3 carriers (Gonsior et al. 2020). Moreover, polyQ-expanded ataxin-3 protein levels correlated with disease stage and clinical severity assessed by SARA (Gonsior et al. 2020). However, this highly sensitive TR-FRET-based immunoassay cannot measure ataxin-3 level in other fluids such as CSF or plasma and should be validated in other cohorts.

In another study, an electrochemiluminescence immunoassay using the Meso Scale Discovery system detected polyQ-expanded ataxin-3 in CSF and plasma distinguishing controls from SCA3 carriers (Prudencio et al. 2020). In addition, this study showed the strong association between *ATXN3* pathological CAG repeat expansion and the rs7158733 SNP located ~132 nucleotides downstream of the CAG repeat (Prudencio et al. 2020) that could facilitate the allele specific ASO treatment.

Another novel single molecule counting (SMC) ataxin-3 immunoassay is able to measure polyQ-expanded ataxin-3 in plasma and CSF (Hübener-Schmid et al. 2021). Clinical correlations (age at onset and SARA score) are reported with plasma polyQ-expanded ataxin-3 levels. Longitudinal data show that plasma levels remain stable over a 1-year period (Hübener-Schmid et al. 2021).

For the other ataxin proteins, specific bioassays are not yet available.

2.5 Oxidative Stress Biomarkers

Oxidative stress has been implicated in several neurodegenerative disorders. Production of abnormally large amounts of reactive oxygen species was reported for SCA3 (Pacheco et al. 2013). This seems to be caused by a dysregulation of major enzymes implicated in antioxidant capacity: superoxide dismutase and glutathione peroxidase (GPx) activities are lower in symptomatic than in pre-symptomatic carriers (de Assis et al. 2017). On the other hand, catalase activity is increased in the serum of SCA3 patients (Pacheco et al. 2013). The correlation of GPx decrease activity with disease severity suggests that GPx may be a reliable biomarker (de Assis et al. 2017).

In SCA2 presymptomatic and symptomatic carriers, glutathione S-transferases (GST) activity is increased by 21.8% and 5.5%, respectively (Almaguer-Gotay et al. 2014). The role of this enzyme is to protect against oxidative stress and prevent

apoptosis. GST increase activity supports the role of free radical damage in SCAs physiopathology.

2.6 Inflammation Biomarkers

Inflammatory genes encoding endopeptidase matrix metalloproteinase 2 (MMP-2) and cytokine stromal cell-derived factor 1α (SDF1α) are upregulated in a cell culture model of SCA3 as well as in human SCA3 pons (Evert et al. 2001). Other proteins involved in inflammation process are significantly increased: amyloid β-protein (Aβ), interleukin-1 receptor antagonist (IL-1ra), interleukin-1β (IL-1β), and interleukin-6 (IL-6) (Evert et al. 2001). Activation of microglia and presence of reactive astrocytes are reported in the brains of SCA3 patients (Evert et al. 2006). Based on these data, a large panel of cytokines has been investigated in a large cohort of presymptomatic and symptomatic SCA3 compared to controls (da Silva et al. 2016). No difference in cytokine levels was detected among the groups except for eotaxin. Higher eotaxin concentrations were observed in asymptomatic carriers than in symptomatic carriers (da Silva et al. 2016). In symptomatic carriers, the level dropped after 1 year (da Silva et al. 2016). One possible explanation may be that the levels of eotaxin released by astrocytes are inversely correlated with disease progression (da Silva et al. 2016).

2.7 Insulin/Insulin-Like Growth Factor 1 (IGF-1) System

Abnormalities in the signaling pathway of the insulin/insulin-like growth factor 1 (IGF-1) system (IIS), including IGF-1, IGF binding proteins (IGFBPs), and insulin, are thought to play a role in the physiopathological processes of neurodegenerative diseases as Alzheimer's disease, HD, and polyQ SCAs (Craft and Watson 2004; Cohen and Dillin 2008; Emamian et al. 2003). SCA3 patients show higher serum levels of IGFBP1 and IGF-1/IGFBP-3 ratio than controls (Saute et al. 2011). Inversely, serum levels of IGFBP-3 (that binds more than 80% of peripheral IGF-1 and increases its half-life) and insulin levels are reduced (Saute et al. 2011). β-cell function is preserved in SCA3 patients and the reduction of insulin level is due to an increased peripheral sensitivity to insulin. Higher sensitivity to insulin and lower insulin levels are both related to earlier disease onset (Saute et al. 2011).

IGFBP-1 levels are correlated significantly with CAG repeat expansion (Saute et al. 2011). IGFBP1 may be a biomarker for SCA3 even though its link with expanded ataxin-3 protein remains unclear. One possible explanation could be the endoplasmic reticulum stress induced by mutant ataxin-3 protein that increases IGFBP-1 production in liver (Saute et al. 2011). Even though IGF1 is not significantly higher, it inversely correlates with the volume of medulla oblongata and pons (Saute et al. 2011).

2.8 Co-chaperone Protein

The carboxyl terminus of Hsp-70 interacting protein (CHIP), a co-chaperone protein, is an endogenous binding partner of the mutant ataxin-3. In SCA3 patients, CHIP level is elevated in both serum and CSF, indirectly reflecting mutant ataxin-3 level (Hu et al. 2019). CHIP correlates with disease severity assessed by SARA and ICARS. The main role of CHIP is protein quality control. Ataxin-3 protein directly interacts with CHIP. The affinity between these two proteins increases with CAG expansion causing a cellular homeostasis dysregulation.

3 Biomarkers in Development

3.1 Brain Cholesterol Metabolism

Deregulation of brain cholesterol turnover and metabolism have been associated with several neurodegenerative diseases. 24-hydroxylase (CYP46A1) is the key enzyme of efflux of brain cholesterol, converting the excess cholesterol into 24S-hydroxycholesterol (24OHC) released in systemic circulation (Leoni et al. 2013). Plasma 24OHC is significantly reduced in neurological disorders as Alzheimer's disease, Parkinson's disease, Niemann–Pick disease type C, multiple sclerosis, and HD (Papassotiropoulos et al. 2005; Kölsch et al. 2009; Shobab et al. 2005; Solomon et al. 2009; Leoni et al. 2002). For HD, 24OHC levels decrease with disease progression and striatal volume loss (Leoni et al. 2013). In SCA3 cerebellum samples, CYP46A1 is reduced (Nóbrega et al. 2019). The overexpression by an adeno-associated virus (AAV)-mediated expression of CYP46A1 decreases the ATXN-3 aggregates by activation of autophagy and leads to motor improvement in SCA2 mouse model (Nóbrega et al. 2019). Plasma 24OHC may be a potential biomarker for SCAs as reported for HD, therefore further investigations should be carry on.

3.2 Metabolic Profile

The serum metabolomics profile shows a difference between symptomatic SCA3 patients and presymptomatic carriers or controls (Yang et al. 2019). In SCA3 patients, there is a downregulation of branched-chain amino acids including valine and leucine, and aromatic amino acids as tryptophan and tyrosine (Yang et al. 2019). These metabolites are precursors of some neurotransmitters (serotonin, dopamine, GABA) and have a role in energy metabolism. Fatty acid metabolism is also dysregulated in SCA3 patients with decrease of saturated fatty acid and increase of monounsaturated and polyunsaturated fatty acid fatty (Yang et al. 2019).

Plasma lipidomic analysis in a cohort of polyQ SCAs showed that SCA7 patients differentiate from other polyQ SCAs patients for some ceramides and phosphatidylcholines (Garali et al. 2018). These lipids are strongly expressed in retina and their deficit may be linked to the retinal alterations characteristic for SCA7 rather than other polyQ SCAs.

For SCA7 patients, another study has reported the decreased of branched-chain amino acids, leucine and valine, as well as of tyrosine, with a good sensitivity to discriminate from controls (Nambo-Venegas et al. 2020). Moreover, when regarding only SCA7 carriers, methionine level differentiates early onset from late onset patients (Nambo-Venegas et al. 2020).

3.3 Micro-RNAs

Several studies investigated micro-RNAs (miRNAs) levels in SCAs patients reporting different results. Lower levels of miR-25, miR-125b, miR-29a, and miR-34b are found in serum of SCA3 patients compared to controls (Huang et al. 2014; Shi et al. 2014). Reduced concentrations of miR-9 and miR-181a from CSF derived exosomes of SCA3 patients are reported (Hou et al. 2019). Three miRNAs-mir-9, mir-181a, and mir-494 are decreased in SCA3 human neurons (Carmona et al. 2017). These three miRNAs interact with the ATXN3-3′ UTR downregulating its expression (Carmona et al. 2017). In SCA3 mouse model, the overexpression of these miRNAs reduces the mutant ataxin-3 expression by translation inhibition and mRNA degradation (Carmona et al. 2017). For SCA7, the plasma expressions of four miRNAs (hsa-let-7a-5p, hsa-let7e-5p, hsa-miR-18a-5p, and hsa-miR-30b-5p) differentiate carriers from controls and seem to have a prognostic value discriminating between juvenile and adult onset (Borgonio-Cuadra et al. 2019).

These data could suggest miRNAs as potential biological markers of disease and therapeutic targets. However, their use does not seem to be possible in the short term.

3.4 Sirtuin-1

Sirtuin-1 is a NAD+-dependent deacetylase taking part in several cellular functions as chromatin modulation, cell cycle, apoptosis, and autophagy regulation in response to DNA damage. In SCA3 mice and in SCA3 patients' fibroblasts, sirtuin-1 mRNA levels are lower than controls (Cunha-Santos et al. 2016). In SCA3 mice, the caloric restriction rescues sirtuin-1 with motor improvement (Cunha-Santos et al. 2016). Sirtuin-1 overexpression activates autophagy and increases the mutant protein clearance. This overexpression results in neuropathological changes: activation of autophagy, decrease in neuroinflammation, and reduction in reactive gliosis (Cunha-Santos et al. 2016).

4 Conclusion

This chapter reviews the available biomarkers in blood and CSF for polyQ SCAs. However, the majority of the evidence are reported for SCA3, the most frequent subtype worldwide, and only few longitudinal studies have been conducted with a lower inclusion of presymptomatic carriers. Still many efforts need to obtain an optimal biomarker with diagnostic and prognostic values, reliable to be used in upcoming gene therapy trials. Neurofilaments light chain seems to be currently the best biomarker, already confirmed in several neurological diseases, with a role to monitor drug administration in spinal muscular atrophy (Olsson et al. 2019) and multiple sclerosis (Kuhle et al. 2019). A great interest there is towards the development of ataxin bioassays that are the specific target of ASOs therapy. Other pathways presented in this chapter require validation in larger cohorts.

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