Fondazione EBRI
Rita Levi-Montalcini Institute

La SUMOilazione proteica come sensore di stress ossidativo cellulare sia in patologie neuronali che nell'aging ed eventuali applicazioni nel settore aerospaziale

Marco Feligioni PhD
Group Leader

LAB: Modifiche post-traduzionali delle proteine e meccanismi di rilascio dei neurotrasmettitori

Effects of Spaceflights on the gene expression in mouse Brain

2022

npj | microgravity

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ARTICLE OPEN

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Characterization of gene expression profiles in the mouse brain after 35 days of spaceflight mission

Jacob M. Holley[1], Seta Stanbouly[1], Michael J. Pecaut[1], Jeffrey S. Willey[2], Michael Delp[3] and Xiao Wen Mao[1]✉

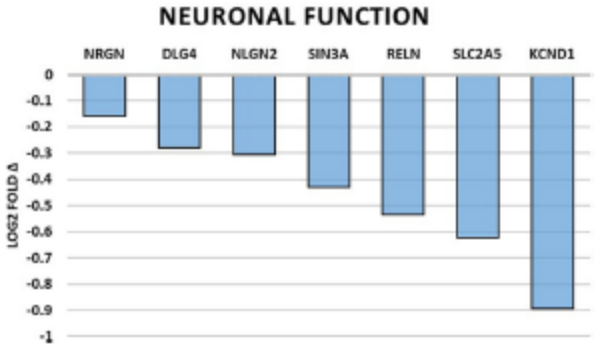


Fig. 1 Spaceflight-induced changes of gene expression related to neuronal function. Bar graph summarizing log2 fold-changes of significantly differentially expressed genes (DEG) ($p < 0.05$) in the flight (FLT) group compared to the ground control (GC) group in genes directly related to neuronal function. $N = 6$/group. p values are calculated using one-way analysis of variance (ANOVA) and Tukey's HSD (honestly significant difference) test. Source data are provided as a Source Data file.

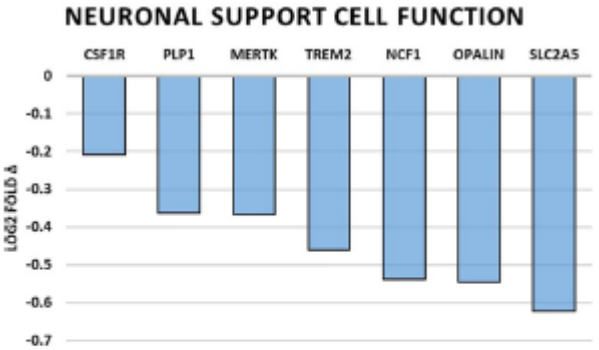
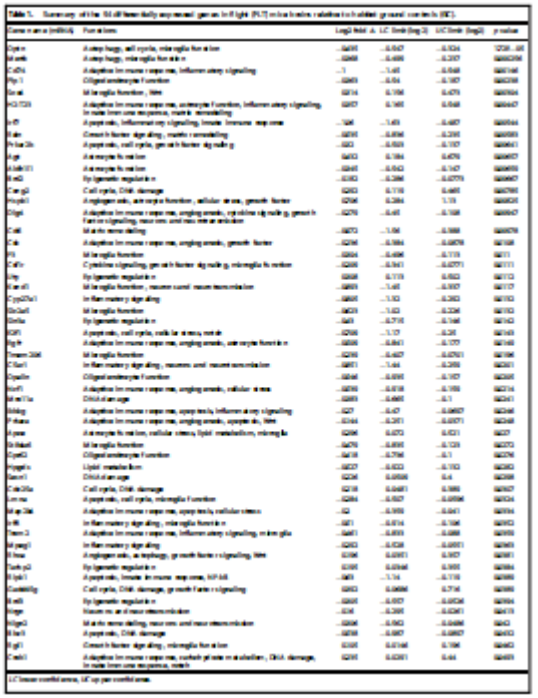


Fig. 2 Spaceflight-induced changes of gene expression related to neuronal support cell function. Bar graph summarizing log2 fold-changes of significantly differentially expressed genes (DEG) ($p < 0.05$) in the flight (FLT) group compared to the ground control (GC) group in genes directly related to neuronal supporting cell function. $N = 6$/group. P values are calculated using one-way analysis of variance (ANOVA) and Tukey's HSD (honestly significant difference) test. Source data are provided as a Source Data file.



Conclusions

Genes related to neuronal function, neuronal cell support, immune function, cellular growth , neuronal plascitity and stress were significantly altered

Effects of Spaceflights on the Brain

2022

Brain Connectometry Changes in Space Travelers After Long-Duration Spaceflight

Andrei Doroshin[1], Steven Jillings[2], Ben Jeurissen[2], Elena Tomilovskaya[4], Ekaterina Pechenkova[5], Inna Nosikova[4], Alena Rumshiskaya[6], Liudmila Litvinova[6], Ilya Rukavishnikov[4], Chloë De Laet[2], Catho Schoenmaekers[2], Jan Sijbers[3], Steven Laureys[7], Victor Petrovichev[6], Angelique Van Ombergen[2,8], Jitka Annen[7], Stefan Sunaert[9], Paul M. Parizel[10], Valentin Sinitsyn[11], Peter zu Eulenburg[12], Karol Osipowicz[1] and Floris L. Wuyts[2]

Frontiers in Neural Circuits

TABLE 1 | Demographic information of cosmonaut and control group subjects.

	Cosmonauts *average (SD)*	Controls *average (SD)*	Two-sample *t*-test (p-value)
Age (years)	45 (5)	43 (6)	0.349
Mission duration (days)	172 (25)		
Previous mission experience (days)	199 (199)		
Preflight MRI – launch (days)	89 (34)		
Return – postflight MRI (days)	10 (3)		
Preflight MRI – postflight MRI (days)	270 (32)	240 (54)	0.099
Return – followup MRI (days)	230 (62)		

Preflight and postflight MRI for the control group represents the two scanning sessions for this group. Statistical comparisons between the two groups were performed using a two-sample t-test (2-tailed). SD = standard deviation.

Quantitive anisotropy measures

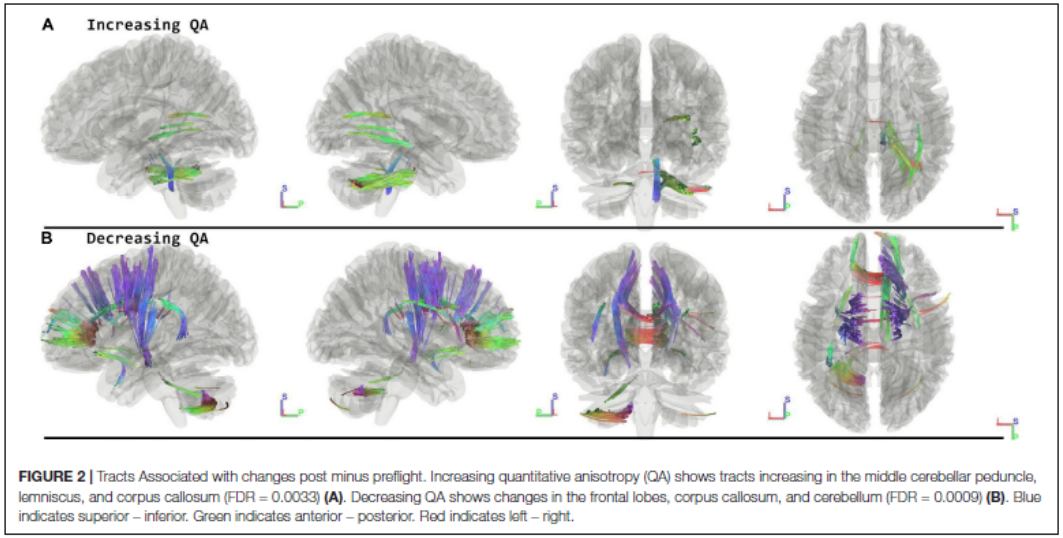


FIGURE 2 | Tracts Associated with changes post minus preflight. Increasing quantitative anisotropy (QA) shows tracts increasing in the middle cerebellar peduncle, lemniscus, and corpus callosum (FDR = 0.0033) **(A)**. Decreasing QA shows changes in the frontal lobes, corpus callosum, and cerebellum (FDR = 0.0009) **(B)**. Blue indicates superior – inferior. Green indicates anterior – posterior. Red indicates left – right.

Conclusions

- Transient brain and intracranial cerebral fluid shift.
- Sensorimotor, language and visual function areas alteration
- Permanent tissue changes (7 months)

Effects of Spaceflights on tumor cells

2021

REVIEW

Journal of Neuroscience Research

Space flight and central nervous system: Friends or enemies? Challenges and opportunities for neuroscience and neuro-oncology

Giovanni Marfia[1,2,3] | Stefania Elena Navone[1,2] | Laura Guarnaccia[1,4] | Rolando Campanella[1] | Marco Locatelli[1,2,5] | Monica Miozzo[6,7] | Pietro Perelli[8] | Giulio Della Morte[3] | Leonardo Catamo[3] | Pietro Tondo[3] | | Carmelo Campanella[11] | Marco Lucertini[9] | Giuseppe Ciniglio Appiani[9] | Angelo Landolfi[9] | Emanuele Garzia[10]

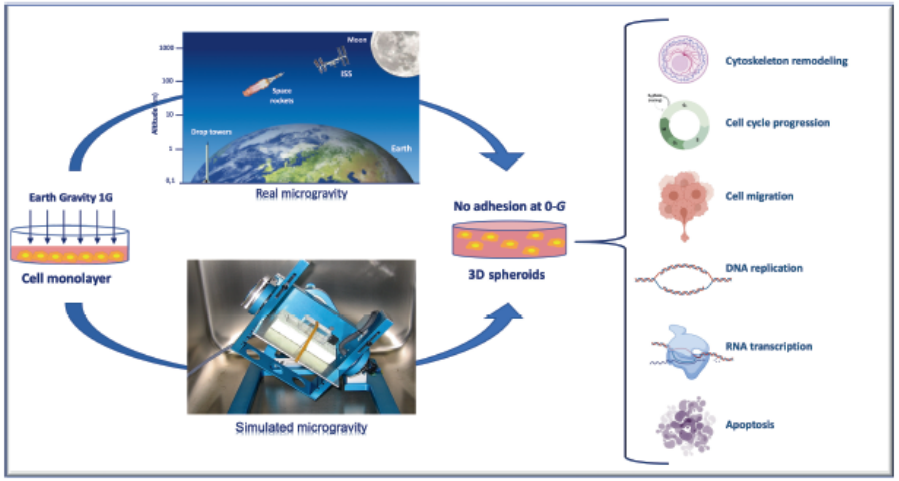


FIGURE 1 Current research platforms to conduct study with real µg in space environment. On the Earth, at 1G gravity condition, cells grow as an adhesive monolayer, whereas in orbit, with the decrease of gravity, cells lose their adhesive property, adopting a floating aspect. The random positioning machine (RPM) is a ground-based device to simulate microgravity, in order to setup spheroid, organoid, and 3D growth cultures to investigate the effect of microgravity on cell behavior, cytoscheleton remodeling, cell cycle progression, cell migration, DNA replication, RNA transcription, and apoptosis.

Effects of microgravity on non-cancer cells:

- mesenchymal stem cells into neurons (BDN, NGF …)
- oxidative stress: in hippocampus, activation of glucocorticoid receptors
- reduction in b-synuclein, protein aggregation
- pyruvate dehydrogenase (PDK-1) regulation of glucose and fatty acid metabolism and homeostasis, (hypoxia and oxidative stress protection)

Conclusions

Microgravity works reducing cellular growth in several tumor cells by promoting cell death

Measuring effects of spaceflights on hBody

life 2022 MDPI

Review

Monitoring the Impact of Spaceflight on the Human Brain

Michael F. Dinatolo [1] and Luchino Y. Cohen [2,*]

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On Earth

Magnetic resonance imaging (MRI),
Positron emission tomography (PET),
Computerized tomography (CT)

Spaceflights

Electroencephalography (EEG),
Functional near-infrared spectroscopy (fNIRS),
Ultrasound

Figure 1. Data collection with an EEG electrode cap onboard the ISS. European Space Agency (ESA) astronaut Andre Kuipers is wearing an EEG electrode cap for the NEUROSPAT investigation. (NASA Image: ISS030E022613).

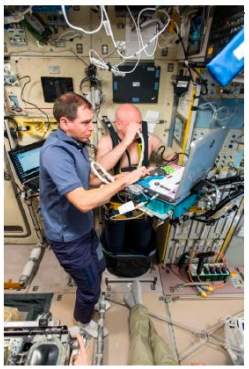
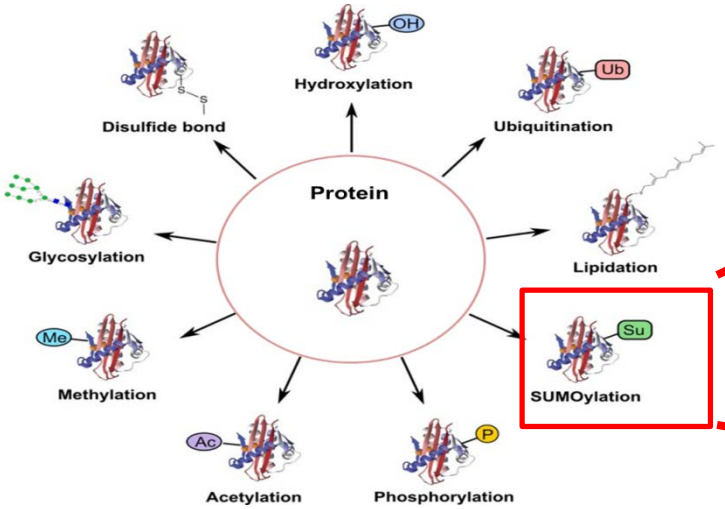


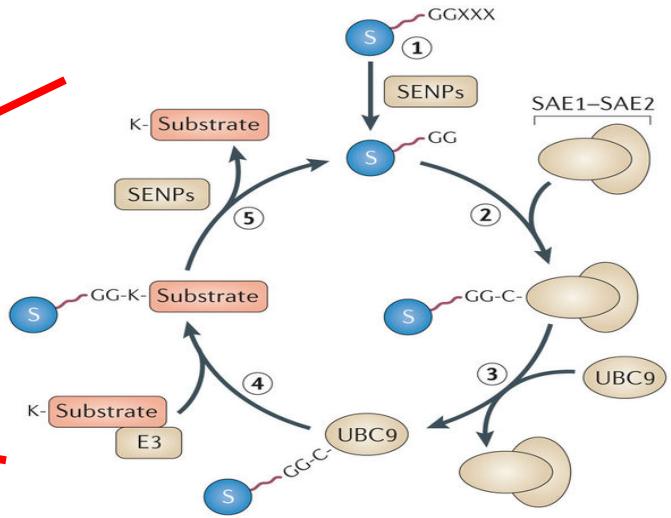
Figure 2. Ultrasound onboard the ISS for measuring fluid shifts. Ultrasound for fluid shift experiments performed on NASA astronaut Scott Kelly (NASA Image: ISS045E015549).

WHAT ABOUT A MOLECULAR BIOMARKER?

Post translational modification (PTMs)

SUMOylation

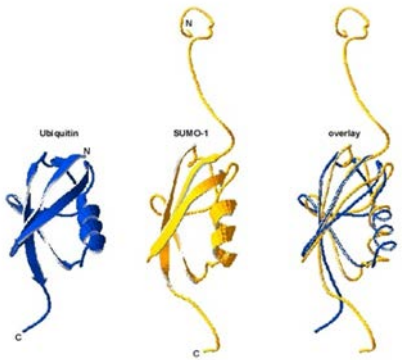




Molecular Characterization of the SUMO-1 Modification of RanGAP1 and Its Role in Nuclear Envelope Association

Rohit Mahajan, Larry Gerace, and Frauke Melchior
Department of Cell Biology, The Scripps Research Institute, La Jolla, California 92037

Nature Reviews | Microbiology



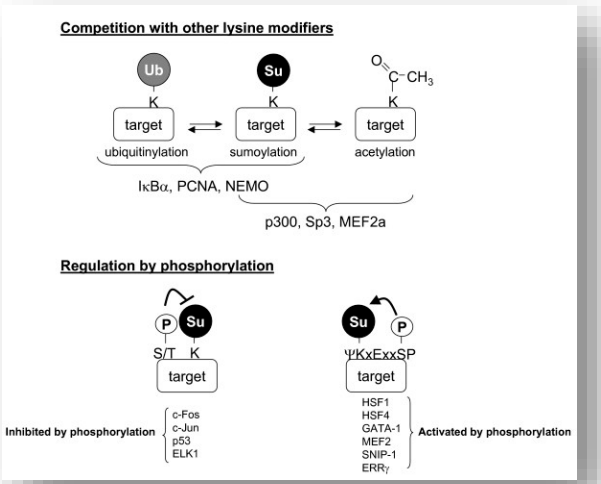
SUMO isoforms

SUMO 1, -2, -3 (BRAIN)

SUMO 4 not in brain

Target protein

ψKxE/D



SUMO: regulating the regulator

Guillaume Bossis and Frauke Melchior

OXIDATIVE STRESS, INFLAMMATION

Neurodegenerative diseases in which SUMOylation is involved

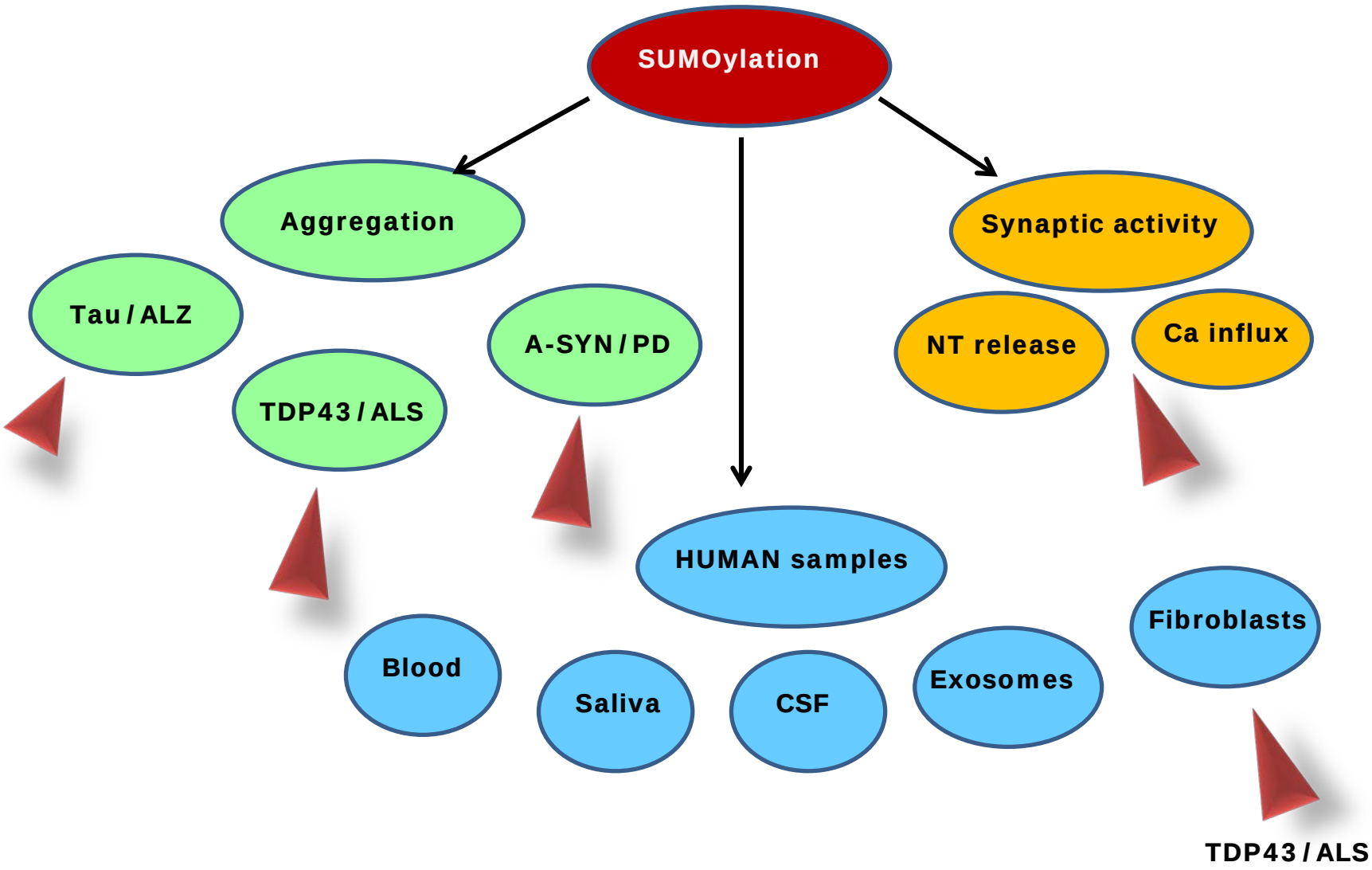
Table 1 Sumoylation in neurodegenerative disorders

Disease	Substrate	Modified residue	Functional impact	Reference
Polyglutamine diseases				
HD	Huntingtin	K6, K10, K15	Negative regulation of Htt97Q aggregation when fused to SUMO; sumoylation increases nuclear targeting and transcriptional repression	Steffan et al. [76]
SBMA	Androgen receptor	K385, K518	Attenuates polyglutamine-mediated aggregation	Poukka et al. [130], Mukherjee et al. [131]
SCA type 1	Ataxin-1	Multiple sites	Mutant ataxin-1-82Q is sumoylated to a lesser extent than WT	Riley et al. [73], Ryu et al. [99]
SCA type 7	Ataxin-7	K257	Negative regulation of mutant ataxin-7 aggregation	Janer et al. [100]
SCAN1	TDP1	K111	Proper sub-nuclear targeting	Hudson et al. [59]
DRPLA	Atrophin 1		Co-expression of SUMO1 and atrophin with expanded poly-glutamine stretches increases its nuclear aggregation	Terashima et al. [132]
AD	APP	K587, K595	Negative regulation of Abeta levels	Li et al. [77], Zhang and Sarge [104]
	Tau	K340	Phosphatase inhibition and MT depolarization increase tau sumoylation	Dorval and Fraser [91]
ALS	SOD1	K75	Increases protein stability and aggregation	Fei et al. [78]
	EAAT2	NA	Accumulation of sumoylated proteolytic fragment of EAAT2 in the nuclei of spinal cord neurons from SOD-G93A mice	Gibb et al. [105], Foran et al. [107]
Synucleinopathies				
PD	α-Synuclein	K96, K102	Impaired sumoylation increases aggregation and toxicity	Krumova et al. [75], Dorval and Fraser [91]
	DJ-1	K130	Dysregulated sumoylation decreases DJ1 solubility	Shinbo et al. [74]
MSA	α-Synuclein		SUMO-positive brain inclusions	Pountney et al. [94]
DLB	α-Synuclein		SUMO-positive brain inclusions	Pountney et al. [94]
NIID	Various		SUMO-positive neuronal intranuclear inclusions of sporadic and familial NIID	Pountney et al. [112], Fujigasaki et al. [113]
Hypoxia	Various			Cimarosti et al. [108]

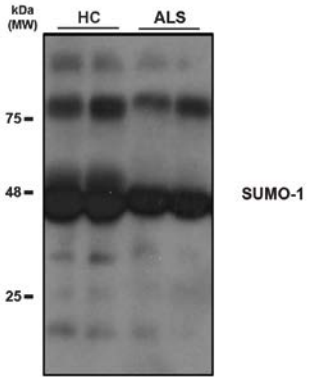
AD Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *APP* amyloid precursor protein, *APP* amyloid precursor protein, *DLB* dementia with Lewy bodies, *DRPLA* dentatorubral-pallidoluysian atrophy, *EAAT2* excitatory amino-acid transporter 2, *HD* Huntington's disease, *MSA* multiple system atrophy, *MT* microtubule, *NIID* neuronal intranuclear inclusion disorder, *PD* Parkinson's disease, *SBMA* spinal and bulbar muscular atrophy, *SCA* spinocerebellar ataxia, *SCAN1* spinocerebellar ataxia with axonal neuropathy, *SOD1* superoxide dismutase 1, *TDP1* tyrosyl DNA phosphodiesterase 1

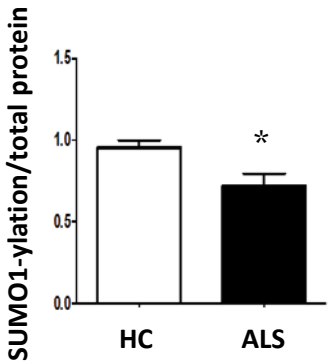
P. Krumova et al. Cell Mol Life Sci. 2013 Jun;70(12):2123-38.

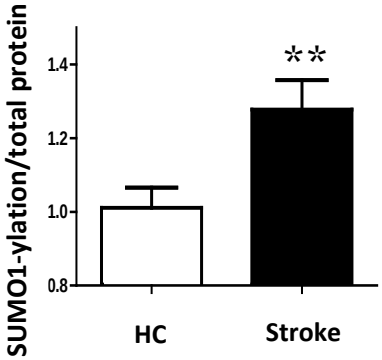
Scientific interests on protein SUMOylation

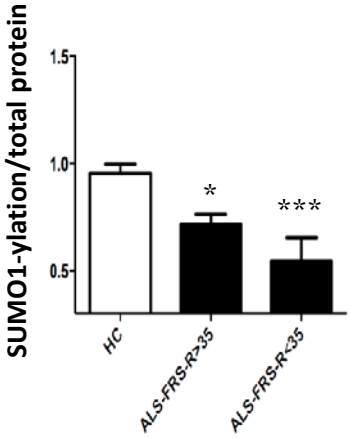


SUMOylation in Human Serum



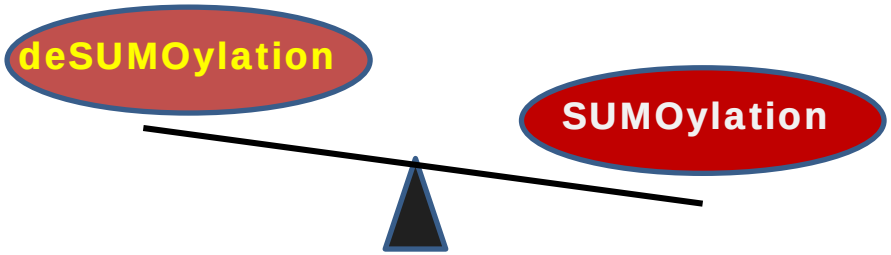






FRS: Functional Rating Scale

Project to evaluate SUMOylation in human blood samples



1. General protein SUMOylation in the blood of astronauts
2. Modification of proteins of the brain
3. Can SUMOylation be a biomarker of oxidative stress in the blood?