NF-kB/c-Rel in peripheral blood mononuclear cells as potential heraldic biomarker of Parkinson's Disease

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Background: A common factor candidate to join neurodegeneration to immune dysregulation in PD is the deficit of NF-kB/c-Rel activity. NF-kB/c-Rel promotes neuroprotection in CNS through transcription of specific anti-apoptotic genes, MnSOD, BcL-xL and UCP4. Of note, mice deficient for the c-Rel subunit develop an aging-related and L-DOPA-responsive parkinsonism, associated with a neuropathology including dopamine (DA) neuron loss in the substantia nigra, neuroinflammation and accumulation of alpha-synuclein (AS) and iron (1). What's more, it is likely that deficient c-Rel function in immune cells may contribute to chronic neuroinflammatory condition in PD. Indeed, besides regulating Th1 response, c-Rel acts as a pioneer transcription factor in driving Foxp3 transcription in the control of differentiation of Fopxp3+ Treg cells (2) which maintain the immune tolerance by suppressing activity of autoreactive T lymphocytes.
Peripheral blood mononuclear cells (PBMC) are proposed to represent a cellular model of disease-related changes in PD brain since these cells express dopamine transporter (DAT), tyrosine hydroxylase, and ubiquitin-proteasome activity modulating AS levels (3-6). Hence, the measurement of specific proteins in PBMCs could provide a non-invasive and effective tool to single out novel molecular signatures serving as peripheral PD biomarkers.
Our preliminary data showed a significant reduction of c-Rel-DNA binding in PBMCs of 23 PD patients when compared to 17 healthy subjects recruited at the IRCCS San Camillo, Venice. These results have been exploited by the University of Brescia to file a patent application. Thereafter, we moved to evaluate a new, larger population of PD patients and relative control subjects to measure the relationship between changes in c-Rel activity and levels of key synaptic proteins, as AS and DAT, in PBMC.

Results: We isolated PBMC from the venous blood of 105 patients and 38 matched healthy subjects of both sexes and between 44 and 86 years of age, recruited at the Neurology Divisions of the University of Brescia. The patients cohort included 90 subjects with Parkinson's disease and 15 with atypical parkinsonism, such as dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration.
We first analyzed the c-Rel activity in PBMCs from 34 idiopathic PD patients and 26 age-matched healthy control. A significant reduction of c-Rel activity was found in PD patients compared to age matched controls, confirming our previous results.
c-Rel activity was also evaluated in 11 patients of atypical parkinsonism and we detected values similar to the control group. The data suggest that the deficit of c-Rel activity in PBMC may be a potential specific marker discriminating PD from atypical parkinsonism.
Ongoing experiments are focused to evaluate the level of DAT and AS, by western blot analyses in PBMC of PD patients and age-matched healthy subjects.

Conclusions: These preliminary data suggest that c-Rel activity analyses could be considered as a potential biomarker for the differential diagnosis between PD and other parkinsonism. Moreover, additional experiments could provide information on whether changes in c-Rel factor and synaptic proteins represent a novel molecular signature of PD, when compared to other movement disorders, and serve as markers for disease diagnosis and efficacy assessment of pharmacological therapies.