TRIM32 and alpha-synuclein: a novel interplay in the neuronal system

Parkinson's disease (PD) is the second most common neurodegenerative disease mainly characterised by the progressive loss of nigrostriatal dopaminergic neurons, resulting in a series of motors symptoms and the formation of intracellular inclusions within the cells, known as Lewy bodies. However, non-motor symptoms such as olfactory deficits appear during the pre-symptomatic phase of the disease and further impact the life quality of the patients. PD is considered a complex disorder deriving from the interaction of both environmental and genetic factors, with 10% of all cases attributed to classical Mendelian inheritance. *Alpha-synuclein* (*snca*) represents one of the most studied PD-related genes, with the protein comprising the main component of Lewy bodies. Although it was described that alpha-Synuclein protein (SNCA) has a strong synaptic function and is involved in the regulation of neurogenesis, we still lack a clear understanding of its cellular functions in physiological and pathological conditions.

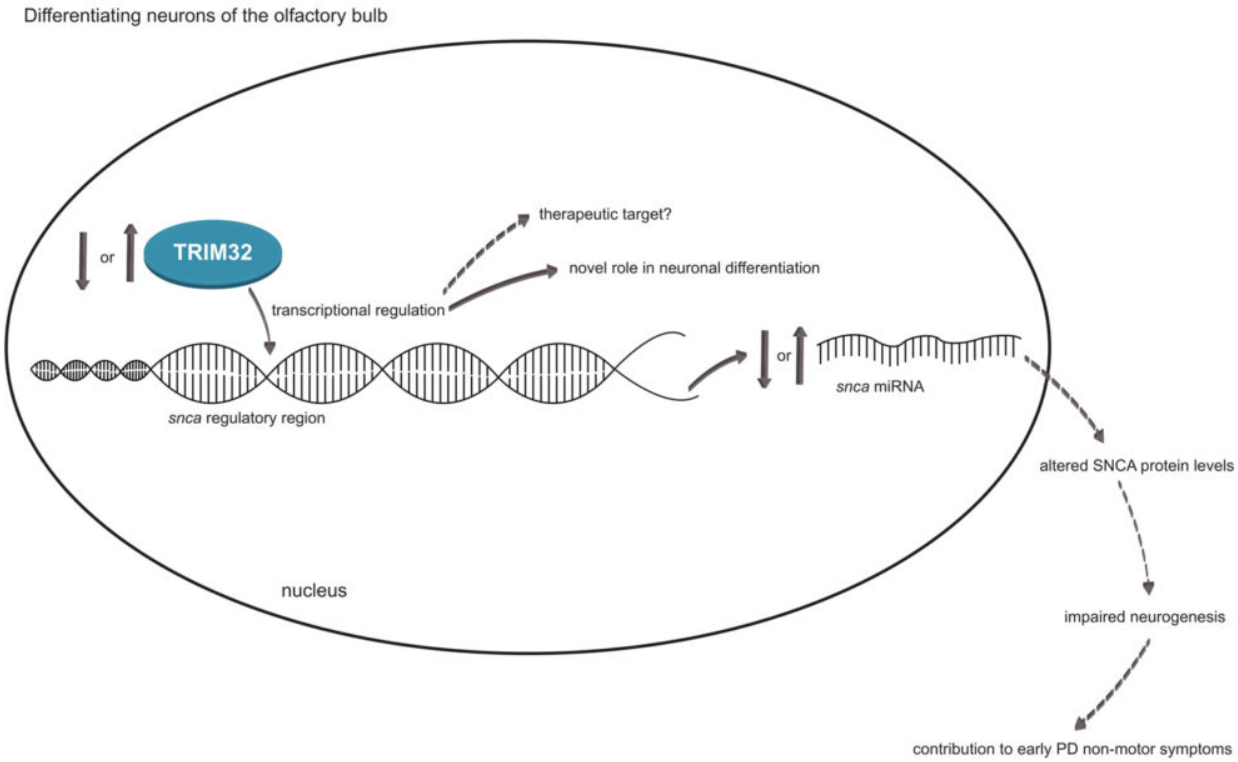

Fig. 1. In the differentiating neurons of the olfactory bulb, TRIM32 is localised in the nucleus. There it is able to bind to the promoter of snca regulating its transcription. Downregulation of overexpression of TRIM32 lead to altered snca transcript levels and have an impact in the neurogenesis process, suggesting a novel role of TRIM32 and snca towards neuronal differentiation. On the other hand, SNCA protein levels may be modulated leading to defects in the adult olfactory bulb neurogenesis and to a possible contribution to early PD-associated non-motor symptoms like olfactory deficits.

Solid lines: established data, dashed lines: hypothesis.

We have previously found that the neuronal cell fate determinant TRIM32 is upregulated upon neuronal differentiation and is necessary for the correct induction of neuronal differentiation both in the embryonic and adult mammalian brains, especially in the cells of adult olfactory system. Cells lacking TRIM32 differentiate slower and present a higher proliferation capacity, resulting in a distorted olfactory bulb neurogenesis. In addition, TRIM32 has been described to translocate into the nucleus during differentiation, ceasing cell cycle by targeting c-Myc for proteasomal degradation, while implying potentially additional roles. In this study we assessed whether this altered localization of TRIM32 influences *snca* transcription. By designing a model based on microarray data we identified a distinct regulatory role of *trim32* on *snca*. Following our model, *in vitro* overexpression of TRIM32 lead to increased transcriptional activity of the *snca* promoter in a concentration and neuronal specific manner. Chromatin immunoprecipitation experiments verified an interaction of TRIM32 with the *snca* promoter. Overexpression or knock down of TRIM32 in neuroblastoma cells (N2a) revealed enrichment or a dramatic decrease respectively of a DNA region corresponding to an essential promoter area of the gene. To investigate the impact of SNCA in neuronal differentiation we used wild type (wt) or TRIM32 knockout (ko) mouse neural stem cells (NSCs) under proliferation or neuronal differentiation conditions. Interestingly, the mRNA levels of *snca* were significantly upregulated in differentiated wt NSCs but not in the TRIM32 ko cells, indicating the impact of TRIM32 on *snca* and how important their relationship is for a balanced neuronal differentiation. Since the olfactory system is one of the first brain regions being impaired in PD, *snca* mRNA levels from different brain regions were analysed in wt and TRIM32 ko mice. A significant reduction was observed only in the olfactory bulb of the TRIM32 ko mice highlighting the impact of TRIM32 on *snca* expression regulation and their possible implication in neurodegeneration. Therefore, the absence of TRIM32 is causing deregulated of *snca* transcripts. In this study we provided evidence of a novel regulatory mechanism of *snca* transcription executed via TRIM32.

By identifying TRIM32 as a novel protein that regulates *snca* transcription new avenues open up offering the possibility of modulating SNCA protein levels and therefore contributing to potential therapeutic approaches against PD.

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Publication

Expression of the Parkinson's Disease-Associated Gene Alpha-Synuclein is Regulated by the Neuronal Cell Fate Determinant TRIM32.
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