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RNA signature in brain lesions of damage or repair in Multiple Sclerosis and the MS-Atlas

We explored mechanistic signatures of different lesion types in the brain of patients with progressive MS: normal-appearing white matter (NAWM), active, chronic active (slowly expanding), inactive and repairing (remyelinating) lesions compared to control brain white matter areas. By comprehensive tissue-transcriptomics and bioinformatics of about 100 brain areas from these different MS lesion types, we have also established a unique public, interactive molecular database of the activated genes: the MS Atlas (Fig. 1).

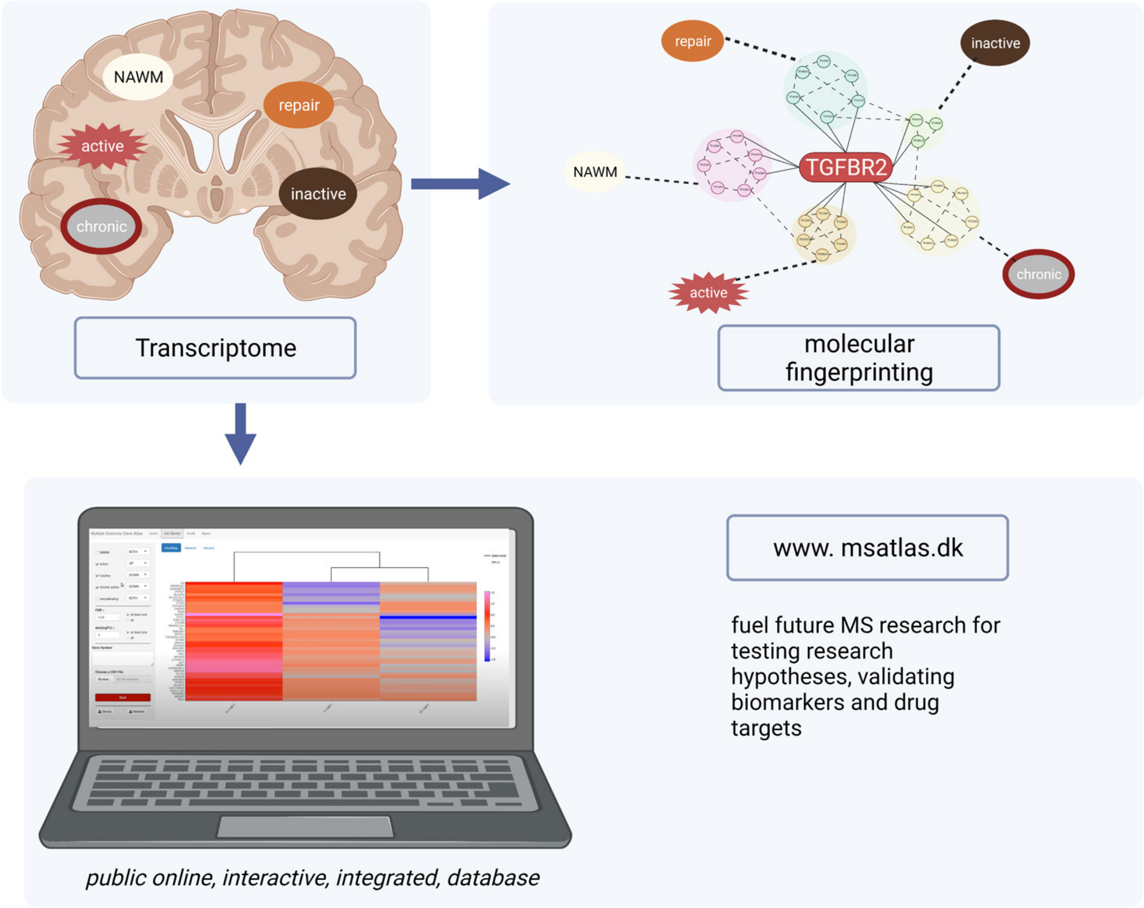

Fig. 1. Establishing molecular signature of brain lesion types in progressive multiple sclerosis. After classifying and microdissecting different lesion types from the MS brain, we performed a comprehensive transcriptome analysis by RNA sequencing, and created the MS-Atlas. Through an unbiased de novo enriched protein-protein network analysis we found that TGFBR2 was a major hub of significantly expressed genes that were shared by the different lesion types. Created by Biorender.com.

Our unbiased search across subsets of multiple lesions provided a discovery of specific molecular signatures validated by different approaches. Among others, we found that the cytokine receptor TGFbR2 was the central molecule in *de novo* molecular networks of common differentially expressed genes (FDR<0.05) in all the different MS lesion types (Fig. 1). We also found that chronic active, slowly expanding lesion had the most unique signature and the highest number of unique significantly expressed genes (n=2213), with approximately 70% related to axonal/neuronal functions (Fig. 2).

Moreover, we used the transcriptome data to create an online database, the MS-Atlas for international MS research. This interactive user-friendly online web-service (www.msatlas.dk) aids also research in other neurological diseases, as it allows researchers and clinicians to (*i*) search for certain molecules of interest, (*ii*) compare gene panels from functional cell/animal studies, and (*iii*) discover mechanistic markers using *de novo* network enrichment in different lesion types (Fig. 1).

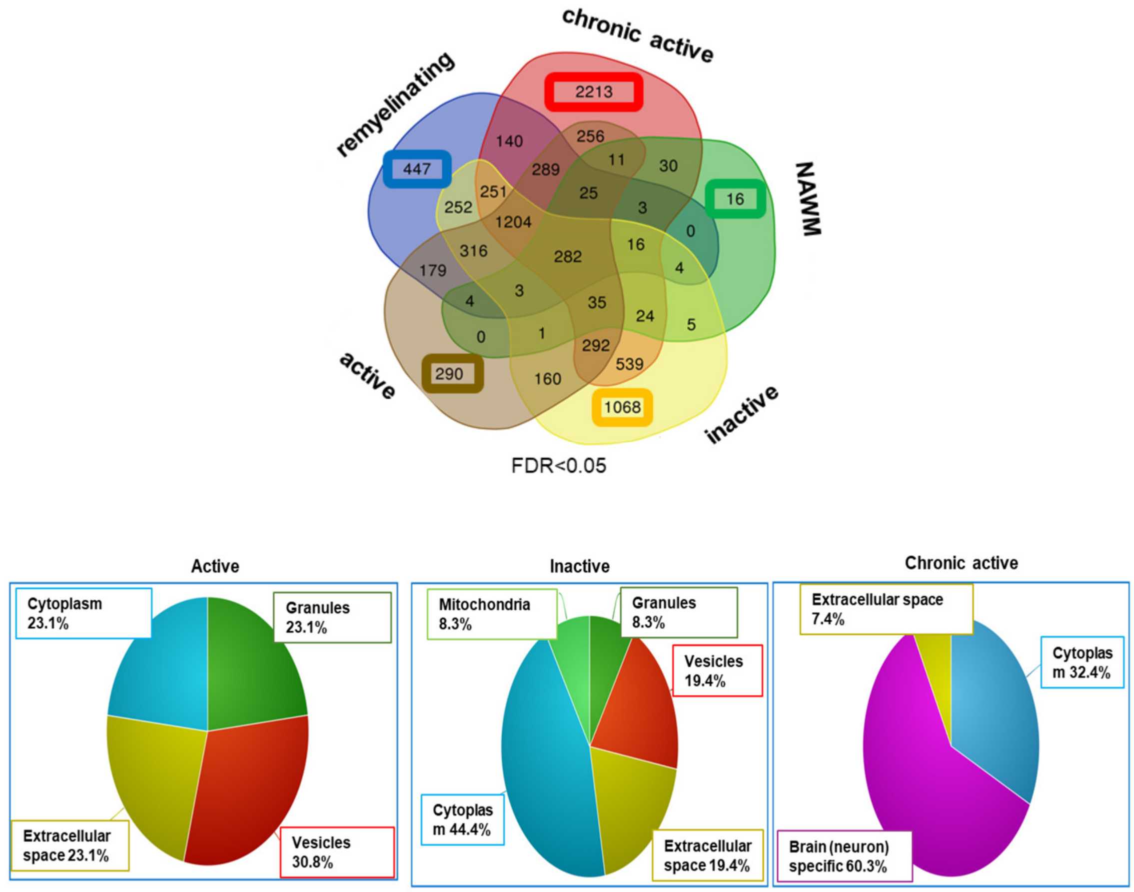

Fig. 2. The uniqueness of cjronic active, slowly expanding lesions in the MS brain. By comparing all the significantly regulated genes across the different lesion types, chronic active lesion had the highest number of unique genes. Chronic active lesions were also highly enriched in neuron/axon-specific biological processes indicated by predefined cellular components. Created by Biorender.com.

In conclusion, we established molecular signature of different lesion types in the brain of progressive MS, and this may help in understanding molecular processes behind chronic, ongoing tissue injury *versus* repair. Our MS atlas is a valuable resource to fuel future MS research, and a new basis for treatment development.

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Publication

Molecular signature of different lesion types in the brain white matter of patients with progressive multiple sclerosis
Elkjaer ML, Frisch T, Reynolds R, Kacprowski T, Burton M, Kruse TA, Thomassen M, Baumbach J, Illes Z.
Acta Neuropathol Commun. 2019 Dec 11