Matrix Metalloproteinases (MMPs) and Their Physiological Tissue Inhibitors (TIMPs) in the 5xFAD Mice Model of Alzheimer's Disease

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Introduction: We have previously demonstrated that MMPs are pleiotropic enzymes involved in nervous system degeneration, plasticity and inflammation. MMPs can also degrade Abeta and possibly influence APP/Abeta metabolism, however very little is known about their involvement in the progression of Alzheimer's pathogenesis. We hypothesize that the balance MMP/TIMP affects Abeta accumulation and that the modulation of MMP activity influences the outcome of the pathology.

Aims:

1) To study the brain expression and activity of MMPs and TIMPs at different ages in the 5xFAD transgenic mice model.

2) To evaluate in these mice the impact of MMP inhibition on Abeta accumulation and the evolution of the pathology.

Methods: Immunohistochemistry, immunoblotting, and zymography techniques are used to evaluate the expression and activity of MMPs and TIMPs, and the accumulation of Abeta. Micropumps are used for chronic ICV infusion of specific MMP inhibitors.

Results: MMP-2 and MMP-9 expression is upregulated mainly in brain neurons at early stages of the pathology (2 months) preceding massive plaque formation. In older animals (6 months) increased levels of these proteinases are found in reactive astrocytes neighbouring amyloid plaques and in the periphery of the plaques. 5xFAD mice characterization of pathology is being conducted to evaluate the effects of specific MMP inhibition in this animal model.

Conclusions: The spatio-temporal pattern of MMPs expression suggests these enzymes may contribute to early events progressively leading to synaptotoxicity/neurodegeneration, and may also be involved at late stages of the pathology in the modulation of the inflammatory response and APP/Abeta metabolism.