

Targeting Inflammation to Inhibit Cognitive Decline in AD

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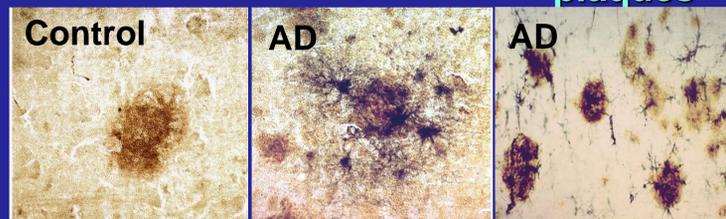
Neuroinflammation and AD

Alzheimer Disease (AD), a neurodegenerative disorder characterized by the accumulation of amyloid- β protein and hyperphosphorylated tau, and neuronal loss, is predominantly associated with aging. While genetic studies have contributed to the development of the amyloid cascade hypothesis, it is clear that amyloid deposits are not sufficient to cause the disease. Evidence for an immune response, including activated glia and complement deposition, in response to amyloid plaque buildup, has led to the hypothesis that complement-induced inflammation is a substantial component in the development of AD dementia, and thus is a target for therapeutic intervention.

Hallmarks of Inflammation in AD

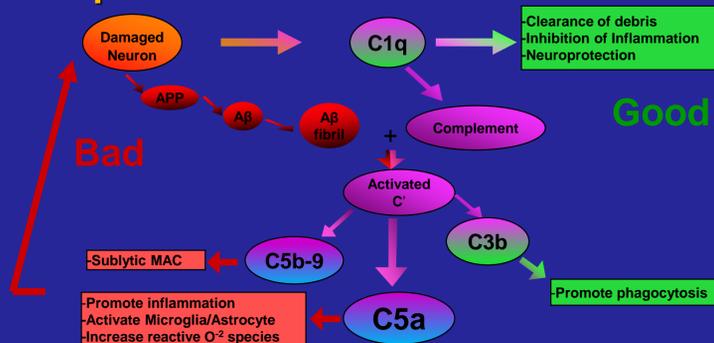
Inflammation is prominent in AD at stages of the disease in which cognitive dysfunction is evident.

Astrocytes and plaques **Microglia and plaques**

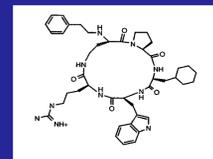


Reactive astrocytes (black, middle panel above) and microglia (black, right panel) are present surrounding fibrillar amyloid plaques (brown) in AD brains but are not found associated with diffuse amyloid plaques (brown) in brains of non-demented patients of the same age (left panel, above).

Disease Mechanism: Complement Cascade is Activated in AD



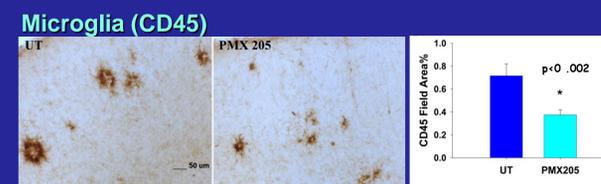
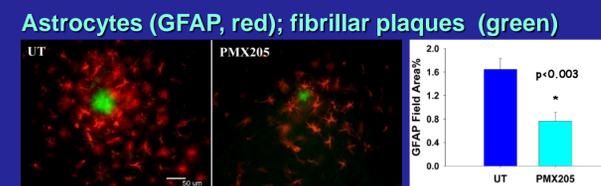
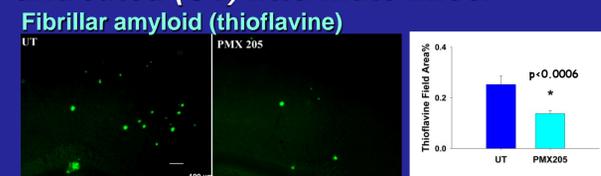
Inhibition of Complement-Mediated Inflammation



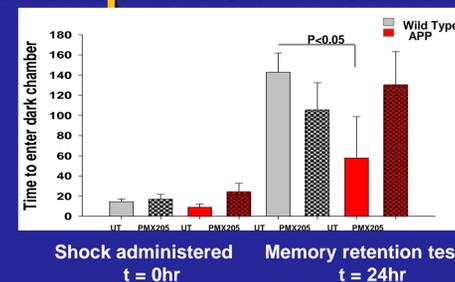
PMX205

- Blocks C5a/CD88 receptor interaction
- No observed side effects

AD model mice given the C5a antagonist (PMX205) in drinking water for 12 weeks show less neuropathology than untreated (UT) littermate mice.

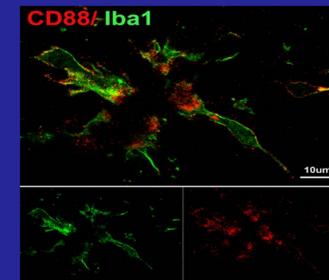


Drug Treatment Results in Improved Memory



Cognition was tested in an avoidance behavior memory task. AD model mice treated with drug performed better 24 hrs. after initial training.

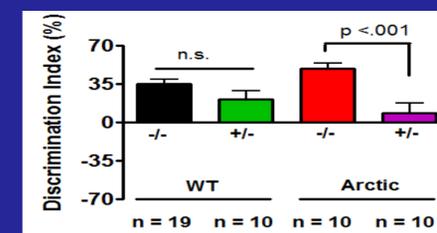
CD88 Expression in AD Mouse Models



The CD88 receptor is found on microglia surrounding plaques and localized predominantly to the plaque-microglia interaction site.

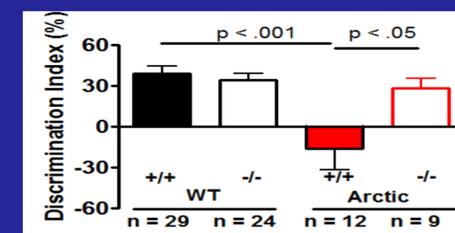
Overproduction of C5a Accelerates Loss of Spatial Memory

Arctic x C5aGFAP – 7 mo.



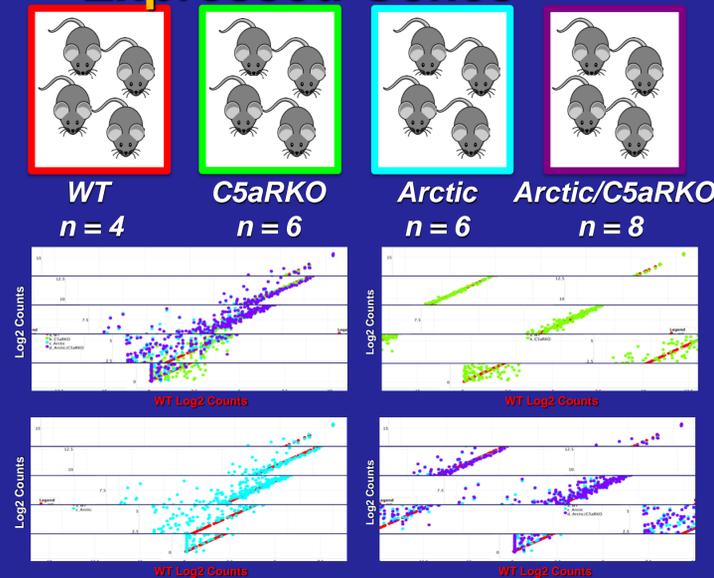
Genetic Ablation of C5aR is Protective

Arctic x C5aRKO – 10 mo.

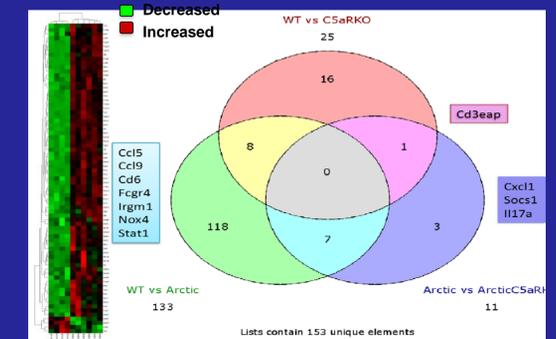


AD transgenic model (Arctic) crossed to C5a overexpressing (top panel) or C5aRKO mice (lower panel) showed worse or better performance, respectively, compared to the Arctic model in a spatial memory task.

Nanostring Analysis to Find Differentially Expressed Genes



Scatter plots of gene expression in brain confirms C5aRKO mice expression similar to WT (top right scatter plot). Abundant differential expression in Arctic mice (bottom left) with Arctic/C5aRKO overlapping with Arctic on most genes (top left and bottom right).



133 genes differentially expressed by Arctic mice relative to WT (left heat map; bottom left circle in Venn diagram). Unique genes differentially expressed between Arctic and Arctic/C5aRKO (purple section of bottom right circle) may be responsible for protective effect seen in C5aRKO mice.

Acknowledgments

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