Cross-activation of innate immunity as driving force in Alzheimer’s Disease.

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• Neuroinflammation is an important component of Alzheimer’s disease pathology and vast number of scientific data indicates a crucial role for activation of the innate immune system in the disease progression.

• Interactions between activated glia and neurons maintain a chronic inflammatory state in affected brain.

• However, mechanism of associations between pathways that induce and sustain low-grade inflammation in degenerating brain are still elusive.

• Cross-activation of RAGE (Receptor for Advanced Glycation End-products) and Toll-like Receptors seems to be responsible for persistent chronic inflammatory state in affected brain.
RAGE in initiation, execution and perpetuation of low grade inflammation in AD brain

Initiation
- Chronic cellular stressors, as: endotoxin, oxidative and carbonyl stress, hyperglycemia, hyperlipidemia cytokines and growth factors.
- Diverse intracellular signaling pathways

Execution
- Cellular oxidative and carbonyl stress
- Proteasomal degradation

Perpetuation
- Expression of: HMGB1, S100, BACE1, RAGE monomers, p65, COX-2, iNOS
- Inflammatory cytokines, adhesion molecules etc.
- Vicious circle: perpetuated stimulation of inflammatory reactions and free radicals generation

MAPK pathways:
- ERK1/2
- JNK
- p38

NF-κB
- NF-κB p50, p65
- IκBα
- Ub K48
- RAGE
- AGE
- Ligands

RAS
- RAS
- Rac1
- Cdc42

Expression of inflammatory cytokines and adhesion molecules.
Conclusions:

- RAGE-TLR cross-activation potentiates inflammatory reactions and sustains low grade inflammation in Alzheimer’s Disease.

- Foreign antigens, are not necessary for the receptors’ cross-activation, since DAMPs rather then PAMPs are responsible for the excitation of RAGE-TLR cooperation.

- Persistent activation of the RAGE compulsively agitates signal transduction pathways of TLR innate immunity receptors. Inclusion of the TLR pathways escalates activation level of transcription factors, thereby enhances inflammatory cytokine synthesis.

- Reduction of RAGE-TLR co-operation requires breaking the vicious circle of self-supporting excitation of the RAGE which is followed by activation of the TLRs pathways.

*(RAGE activation cycle could be broken, for instance: by application of antibodies against the receptor, small synthetic inhibitors of the receptor, by infusion of sRAGE (?) or blocking of ligand interaction with the receptor (e.g. with desulfated heparins).*
• For the pathomechanism of Alzheimer's disease it is also important that RAGE activation markedly increases the Aβ content in the brain, also inside cells, in neurons and in glial cells

(RAGE promotes the NF-kB induced transcription of beta secretase - BACE-1 followed by intracellular amyloidogenic degradation of the APP).

• On the other hand, RAGE avidly binds Aβ, which is a regular, common ligand for this receptor; it accelerates the vicious circle of inflammatory reactions.

• Lowering the level of RAGE activation and silencing of RAGE-TLR cooperation are important goals of therapeutic strategies, whose achievement should significantly slow the progression of Alzheimer’s neurodegeneration and/or stabilize clinical symptoms of the disease.

Thank you for your attention.