INFECTIONS CONTRIBUTE TO PROTEINOPATHIES IN NEURODEGENERATIVE DISEASES AND IN SOME POST-VIRAL PERSISTENT SYMPTOMS

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TAKE-HOME MESSAGES

1. INFECTIONS HAVE THE POTENTIAL TO CONTRIBUTE TO NEURODEGENERATIVE DISEASES (ND), LIKE ALZHEIMER'S DISEASE (AD).
2. BOTH NEUROGENESIS AND NEURONS (OR COMPONENTS OF THE NEUROVASCULAR UNITS) MUST BE AFFECTED TO CAUSE A ND.
3. IMMUNOSENESCENCE, IMMUNODEFICIENCY OR INFLAMMATION CAN ACCELERATE INFECTION-RELATED COGNITIVE DECLINE.

BACKGROUND

- Co-infection with herpes simplex virus type 1 (HSV-1) and cytomegalovirus (CMV) produces an odds ratio of 5.662 for the risk of developing AD[1], comparable to that of APOE.
- Even if infections have long been suspected to contribute to ND, they however are generally not included in prediction models[2].
- Effective treatments already exist for many infections, so some cases of ND could be prevented[3].

GOAL AND METHODS

- We propose a simplified theoretical model for proteinopathies and ND that considers the contribution of infectious agents, based on a targeted literature review of cellular mechanisms affected by HSV-1, CMV and AD.

FIGURE I - NEURONS AND UNFOLDED PROTEIN RESPONSE (UPR)

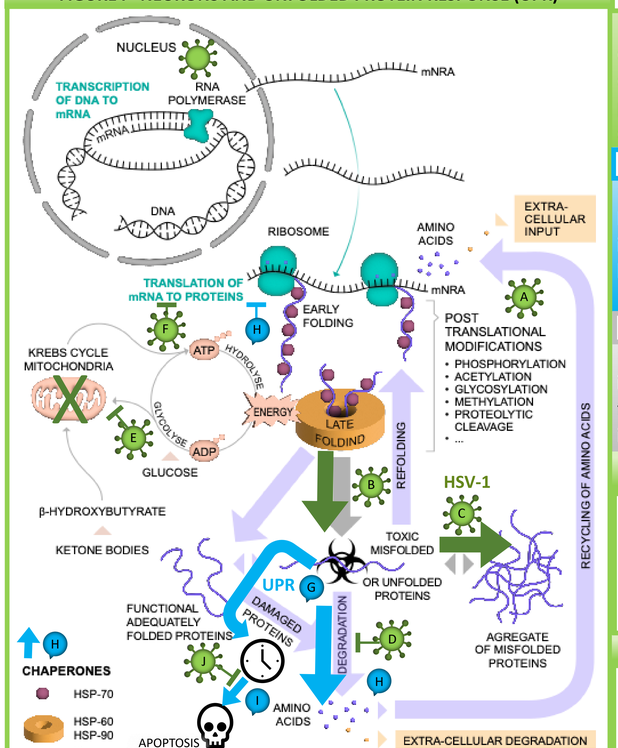


FIGURE I NEURONS AND UNFOLDED PROTEIN RESPONSE

✷HSV-1 induces cellular changes in the neurons consistent with AD rendering the neuron dysfunctional. (Hyperphosphorylation[4,5] A, increased protein misfolding[6] B, increased aggregation[7] C, decreased degradation[8,9] D, mitochondrial dysfunction[10] E, translation halt[11] F, etc.)

✷The protein misfolding G triggers the unfolded protein response[12] (UPR) H that initiates apoptosis I if misfolding is detected for a prolonged period[12].

✷In return, HSV-1 J strongly inhibits apoptosis[13].

FIGURE II NEUROGENESIS CYCLE

✷In the neurogenesis cycle, the dysfunctional neuron K cannot be replaced by a healthy one as HSV-1 inhibits the apoptotic cascade[13] L that its presence M has generated.

✷The neural stem cell pool can be depleted by both CMV N and HSV-1 O causing neural stem cell apoptosis[14] and by CMV P inhibiting their divisions[14].

✷HSV-1[14] Q and CMV[15] R both interfere with the maturation of progenitors into neurons.

✷HSV-1 S promotes differentiation into astrocytes instead of neurons[14].

FIGURE III IMMUNE SYSTEM

✷The immune system T helps to maintain latent infections[16,17], whose reactivation and proliferation are triggered by factors U such as inflammation[18], infections (like COVID-19)[19], and so on[20].

✷Some viruses, such as CMV[21] can provoke immunodeficiency or immunosenescence V enabling the reactivation and proliferation[22] of latent infections.

✷The chronic inflammation produced by CMV W keeps HSV-1 active[22] and vice versa[23] X.

FIGURE II – NEUROGENESIS CYCLE

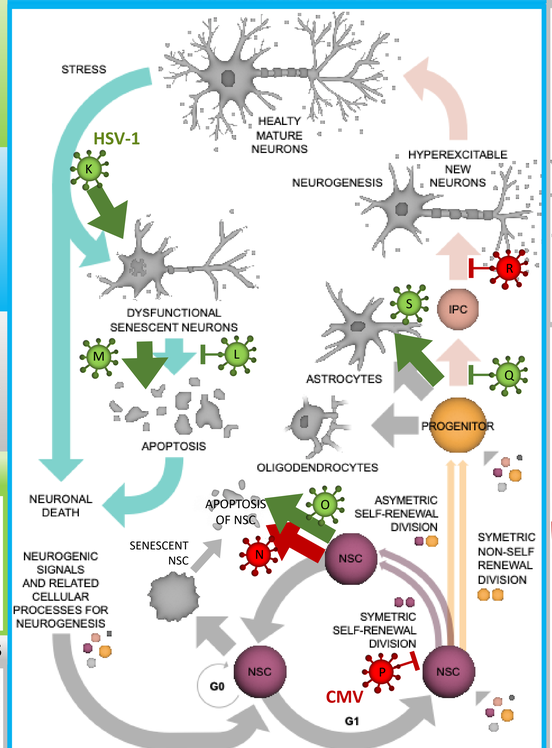
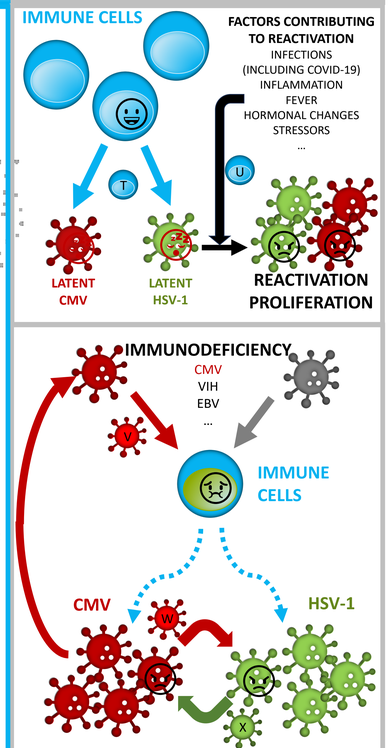


FIGURE III – IMMUNE SYSTEM



CONCLUSIONS

- Our simplified theoretical model can explain why, co-infection with HSV-1 and CMV can lead to AD.
- This model can also be used to understand the impact of other risk factors and infectious agents.
- Reactivating latent infections (HSV-1 and CMV) by triggers such as COVID-19[19] may cause proteinopathies and ND. This mechanism probably adds to those already suspected, such as autoimmunity, to explain some persistent post-viral symptoms.

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VIDEO

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REFERENCES