Polysulfates as treatment option in cerebral malaria?

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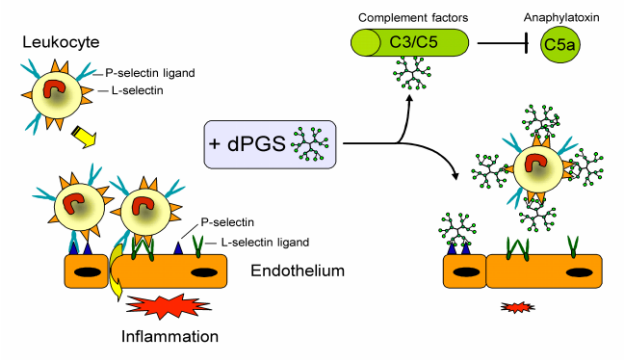

Abstract:

In this joint project together with the sub-projects A6 (Haag) and B7 (Dernedde/Tauber) the impact of synthetic polysulfates as multivalent and multitarget anti-inflammatory compounds will be investigated in a murine model of cerebral malaria (CM).
Infection of susceptible mouse strains with *Plasmodium berghei* ANKA (PbA) is the gold standard model of CM that shares some characteristics with the human disease. CM in both, mice and men involves the sequestration of leukocytes in brain capillaries. It has been previously demonstrated in the murine PbA infection that CM is mainly caused by an unbalanced immune response, involving the production of pro-inflammatory cytokines such as TNF-α and IFN-γ. Thus, in addition to anti-parasitic drugs, immune modulatory therapies might hold great potential for the treatment of CM.
In a first pilot study, polysulfates will be applied to C57BL/6 mice by i.p. injection, and mice will be infected i.p. with PbA loaded erythrocytes. Parasitemia will be determined in Giemsa-stained blood smears from tail blood and mice will be monitored for signs of CM. It is expected that polysulfates modulate the inflammatory process during the course of malaria, thus they might impact the incidence of CM in treated mice. In that case, the mechanism of CM protection will be analyzed in detail. To this end, the brain sequestration of T cells will be studied by flow cytometry of brain homogenates. The production of cytokines (such as TNF-α, IFN-γ, or IL-10) and other effector molecules (such as perforin, granzyme B) of brain-sequestered leukocytes will be detected by intracellular flow cytometry and qRT-PCR of brain tissue. Brain inflammation will also be determined by histopathology and immune histochemistry. In addition, the systemic immune response will be assessed by measuring chemokine and cytokine levels in sera of PbA-infected mice using the cytometric bead array. Furthermore, the expression of co-stimulatory molecules and activation markers by antigen-presenting cells and T cells in the spleen will be measured to elucidate whether polysulfates impacts early T cell activation.
In accompanying *in vitro* assays defined signaling pathways will be screened by PCR arrays, molecular targeting of polysulfates analyzed by SPR and MST, and cell invasion and migration monitored in real time by impedance measurements.
This study will reveal the impact of polysulfates on the modulation of immune-mediated brain inflammation during malaria and elucidate whether these compounds represent promising candidates for the treatment of CM.

Publication/s:

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