CRC654 TPC7 (Köhl/Autenrieth):

Interactions between sleep and complement-driven regulation of intestinal dendritic cell functions

The cross-talk between complement and other innate immune sensor systems, like the Toll- (TLR) and Nod-like receptors (NLR) regulates antigen-presenting cells (APCs) functions at the interface between innate and adaptive immunity. We found a circadian rhythm for complement and observed its regulation by sleep. Previously, the NLR ligand muramyldipeptide (MDP) has been identified as a sleep-promoting factor in humans and animals, which accumulates during the active period to eventually induce slow wave sleep (SWS). The source of MDP is still unknown. It has been suggested that intestinal bacteria enter the lamina propria (LP) and that bioactive MDP is released upon bacterial degradation, which in turn triggers the release of sleep-promoting cytokines including IL-1□ and TNF-□. In addition, viable bacteria can be found in mesenteric lymph nodes (MLN) following sleep deprivation. We propose that intestinal APCs play an important role in this context, as they are known to sample and digest bacteria from the intestinal lumen. We further propose that APCs and their regulation by complement, TLRs and NLRs are simultaneously subjected to a top-down control by central nervous sleep and circadian processes. In the upcoming funding period, we aim to define the impact of sleep on the frequency and function of circulating, intestinal tissue and secondary lymphoid APCs with a particular focus on the crosstalk between innate sensing systems. In addition, we will assess the impact of intestinal bacterial colonization/translocation on the sleep-wake cycle.

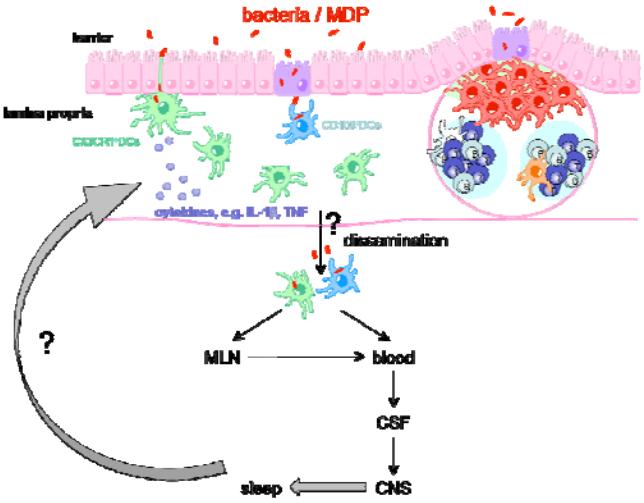

Figure 5. Regulation of sleep by the bidirectional interaction between immune cell regulation and central nervous sleep processes. In this model, monocytes and DCs traffic between the circulation and the in-testine. In the intestine, they become activated through PRRs, take up bacteria and kill them thereby releasing MDP and sleep promoting cytokines such as IL-1β, TNF-α and IL-6. Those substances gain access to the CNS through the blood stream and promote sleep. In turn, sleep affects the migration of monocytes and DCs and prevents bacterial dissemination.