Title: Modeling of Cytokine Signaling in Microglia Reveals Distinctive Roles of TGFβ and IL-10 in Coordinating the TNFα Response to LPS

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Neuroinflammation due to glial activation has been linked to many CNS diseases, including Alzheimer's disease, epilepsy, neuropathic pain, and neurogenic hypertension. While etiologies vary, correlation between neuroinflammation and disease suggests that CNS inflammation may underlie the genesis and/or perpetuation of many pathological states. Because precision in the mechanistic understanding of how intercellular cytokine interactions coordinate the inflammatory milieu is limited in statistical analyses of expression data, we employed a dynamic modeling approach that permits the assessment of system control mechanisms using robustness analyses and targeted perturbations. We developed a microglial cytokine interaction network model to assess potential novel mechanisms of glial activation by employing Differential Equations. The model has 12 activating connections (e.g., TNFα promotes TGFß production), and 12 inhibitory connections (e.g., TGFß inhibits TNFα production), all of which were validated based on available literature. A model fit to cytokine data from LPS-stimulated cultured microglia demonstrated that the model captures the dynamics of experimentally observed regulatory interactions. Variance-based parametric sensitivity analysis suggested that that TNFα is highly sensitive to negative feedback from TGFß and IL-10. Consistent with experimental data, the model showed tolerance in the TNFα response to repeated doses of LPS. While both TGFß and IL-10 inhibit TNFα via feedback, IL-10 knockout (KO) enhanced TNFα tolerance whereas TGFß KO hyper-sensitized the TNFα response to repeated LPS stimuli. The contrasting effects of TGFß versus IL-10 occurred because the IL-10 KO enhanced the initial TNFα peak response, which resulted in subsequent TGFß activation and robust negative feedback, thereby rendering TNFα unresponsive to a second dose of LPS. Thus, IL-10 decreased tolerance by restraining the influence TNFα on TGFß. The mechanism of TNFα tolerance to LPS involved TGFß up-regulation following the initial LPS dose, consistent with data. Simulations examining adaptation of the TNFα response to LPS suggested that TGFß controls adaptation by modulating the steady-state response to LPS, with negligible effect on the peak TNFα response. In contrast, IL-10 primarily controlled the TNFα peak amplitude following LPS, with less effect on adaptation. In summary, our model simulations and analysis results predict that TGFß and IL-10 have prominent and contrasting roles in regulating microglia activation, suggesting potential for targeted therapeutic interventions against neuroinflammation.

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