

Targeted Peptide Therapies: A New Paradigm in HIV Treatment?

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Toll ligands and their receptors (TLRs) play an important role in innate immunity, promoting innate immune responses prior to the transition to a more specific, adaptive immune responses. TLRs recognize pathogen-associated molecular patterns (PAMPs). If uncontrolled, TLR dependent-activation of B or T lymphocytes could play a particularly important role increasing the likelihood of chronic inflammation, characteristic of many forms of chronic autoimmune or inflammatory diseases that arise in certain individuals subsequent to pathogen-driven infectious diseases. Different TLRs cause different responses in cells. Here we demonstrate that activation of TLRs 2, 4, and 9 results in expansion of large numbers of activated B cells that express ectopic CLIP with maximal ectopic expression occurring in most cases at 3-5 days post TLR activation. In contrast, when B cells are activated by the TLR-3 ligand Poly I:C, B cells exhibit a peak increase in ectopic CLIP at 24 to 48 hours followed by a dramatic decline in cell surface CLIP expression by 72 hours. Co-culture of CLIP⁺ B cells with total spleen cells results in expansion of CD4⁺ T regulatory cells (Tregs), increased numbers of conventional CD4⁺ T cells, and expansion of CD8⁺ T cells. By injecting the TLR ligands without and/or with a computationally derived, high affinity peptide (one predicted to have higher affinity for the MHC class II alleles expressed on B cells) than CLIP, we observed that peptides caused a dramatic decreased cellularity in both lymph nodes and spleen, a drop followed by a gradual, but steady increase in total CD4⁺Tregs that increased daily over time through at least 5 days, a significant increase in CLIP⁺ B cell death, an increase in total percent CD4⁺ T cells, and a significant peptide-dependent expansion of CD8⁺T cells. These results suggest that peptide displacement of CLIP promotes death of non-specifically activated B cells and focuses the immune response on the infecting pathogens thereby promoting antigen specific, MHC restricted adaptive immune response and preventing chronic activation of non-specifically activated lymphocytes, a characteristic of chronic inflammatory diseases.