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## **PATHOGENESIS OF AIDS - CONNECTING VIRAL REPLICATION TO DISEASE IN THE NON-HUMAN PRIMATE MODEL**

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**BACKGROUND:** AIDS differs from most other infectious diseases in that the advent of clinical disease is delayed for years despite continuous, high-level HIV replication. Although it is clear that HIV replication underlies the development of overt disease, the slow or delayed tempo of progression implies that host mechanisms must participate in the pathogenetic sequence—a conclusion that is underscored by the finding that natural, non-human primate hosts of the related (and equally cytopathic) simian immunodeficiency viruses (SIV) may in fact manifest high continuous viral replication with no discernable disease in their lifetime. Despite more than 2 decades of investigation, the critical pathophysiologic mechanisms that “connect” HIV replication to immunodeficiency are still undetermined, and controversy exists as to the degree to which direct viral cytopathogenicity on CD4<sup>+</sup> T cells, indirect viral effects on CD4<sup>+</sup> T cells, or non-CD4<sup>+</sup> T cell-related mechanisms participate in the development of immune dysfunction. Rhesus monkeys infected with CCR5-tropic SIV<sub>mac</sub> develop a terminal disease that is temporally accelerated, but otherwise highly analogous, to human AIDS.

**METHODS:** Over the past 5 years, we have undertaken the detailed, systemic analysis of rapid, slow and non-progressive infections in this model so as to identify the immunologic factors most closely associated with the onset of symptomatic immunodeficiency.

**RESULTS:** Our analyses strongly implicate the inability to maintain CD4<sup>+</sup> effector-memory T-cell populations in extra-lymphoid effector sites above a crucial threshold as the proximate mechanism in the development of overt AIDS. However, the primary determinant of this CD4<sup>+</sup> effector-memory T-cell homeostasis does not lie in the effector memory populations themselves, or in the effector sites, but rather in the regenerative central memory CD4<sup>+</sup> populations in secondary lymphoid tissues.

**CONCLUSIONS:** Proliferative failure within and gradual depletion of these central memory populations appears to be the primary determinant of rapid and chronic onset AIDS, respectively. This talk will examine the likely mechanisms involved in CD4<sup>+</sup> central memory T cell “failure,” and discuss the implication of the “2-step threshold” hypothesis for development of new immunotherapeutic interventions in this disease.

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