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Role of Fyn and C-cbl in SEB -mediated signaling in memory CD4+ T cell.

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Fyn is an important protein tyrosine kinase in the TCR mediated signaling pathway. Previous studies showed that the superantigen, Staphylococcal enterotoxin B (SEB) induces robust activation of naïve CD4 T cells but induces tolerance /anergy to memory CD4 T cells. Interaction of SEB with the antigen receptor on T cell (TCR) leads to altered or impaired signal transduction in memory cells, due to a failure to activate a critical tyrosine kinase, ZAP-70. During normal cell activation, ZAP-70 associates with specific plasma membrane microdomains called “lipid rafts” and also becomes physically coupled to the TCR at the junction between the T cell and the antigen presenting accessory cell (immunological synapse). Upon interaction with the TCR, ZAP-70 is normally phosphorylated by the src kinase, Lck, which leads to activation and continuation of signaling cascade. In SEB treated memory cells, ZAP-70 does not form the critical coupling with the TCR and therefore does not become accessible to Lck. Further Fyn activity is elevated in SEB treated memory, but not naïve cells. Also, the activity of c-Cbl, a negative regulator of T cell receptor-mediated signaling, was increased in SEB-treated memory cells. Based on studies, which showed that Fyn is constitutively associated with c-Cbl, it was proposed that Fyn promotes T cell anergy through c-Cbl. It was shown further that down regulating Fyn activity either by using pharmacological inhibitors or by using Fyn knockout mice as a source of memory T cells restores memory cell activation in response to SEB and also promotes proper spatial associations between ZAP-70 and the TCR.