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Systems biology of T-cell signalling

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The development of a predictive model of T-cell activation is challenging due to the unique nature of T-cell activation, which exhibits sensitivity, specificity, and antagonism. The benefit of developing such a model is that it can be used to predict how T-cells respond to any combination of presented ligands, with eventual applications to T-cell immunotherapies. We synthesise the existing models of T-cell activation under a consistent framework of non-linear differential equations such that they can be compared to each other. We show how the models can be related to experiments by simulating the T-cell response to the presentation of ligands of varying affinities and number. Further, we investigate T-cell activation when ligands are co-presented. We show preliminary experimental results that aim to test these models using T cells expressing a high affinity variant of the 1G4 TCR binding to a panel of pMHC ligands that span 5 orders of magnitude in affinity. By performing detailed dose-response assays that include co-presentation of multiple ligands we hope to further refine the mathematical models.

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Genic variants of adapter molecules in leukemia

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Leukemia is a cancer where mature and precursor leukocytes present an uncontrolled proliferation, and that classically classifies like lymphoid or myeloid by the kind of cellular population affected, and, like acute or chronic by their clinical evolution. Nowadays, acute leukemia is one of the most prevalent malignancies in Mexico, both in adults and children. Moreover, etiology of leukemia is diverse, and genetics aspects are considered important risk factors for their appearance. One of these mechanisms is a poor anti tumoral response, by defects in the signaling that activates lymphocytes T CD8+ and Natural Killer (NK) cells. Receptors in these cells are regulated by adapter proteins like DAP12 and DAP10. DAP12 and DAP10 are codified by genes with diverse polymorphism, most of them of single nucleotide (SNP). Therefore, could exist an association between polymorphism in these molecules, and the predisposition and spread of leukemia. The aim of the study is to identify if one or more SNPs in DAP12 or DAP10 are associated with acute leukemia. Through real time PCR we genotyped, until the date, the frequency of two SNPs in DAP12 (C3730T and A3766C) and two more in DAP10 (A38C and C891T) in a group of Mexican mestizo patients attended at the Mexican Social Security Institute (Spanish: Instituto Mexicano del Seguro Social, IMSS) with acute lymphocytic leukemia (ALL; $n = 70$) and acute myeloid leukemia (AML; $n = 50$), compared against a group of healthy donors ($n = 250$). For C3730T and A38C we haven't seen any variation, while to C3730T and C891T the genotype and allelic frequencies are similar in cases and controls, with an OR = 0.8293 (95% CI = 0.0854–8.0492) and $P = 0.8720$, and, an OR = 0.5748 (95% CI = 0.0688–4.8005) and $P = 0.6048$, respectively, comparing ALL alongside controls, presenting no significant difference. SNPs in DAP12 and DAP10 aren't presented as risk or protective factors in the development of leukemia.