Elliot Soomro, T4, VT20
el1422so-s@student.lu.se

Cancer-Germline Antigen Expression Discriminates Clinical Outcome to CTLA-4 Blockade

Inhibition of CTLA-4, an immune checkpoint which downregulates the immune response, is an effective treatment for melanoma. Although, in some cases, patients do not respond well to treatment and determinants for a favorable response have been ambiguous. Interestingly, this study identified a collection of genes which predicted resistance uniquely to therapeutic inhibition of CTLA-4, which would justify poor treatment outcomes in a subset of melanoma patients. Furthermore, these findings imply a possible enhancement of customization of treatment strategies based on genetic determinants, which would be paired with patients that are more likely to respond.

In the study, RNA sequencing data from melanoma biopsies together with data from The Cancer Genome Atlas were analyzed for specific cancer-germline antigens. The result was overexpression of some genes at a specific locus on the X chromosome. Most notably, the findings included a viable association of a collection of genes, titled “anti-CTLA-4 resistance associated MAGE-A (CRMA) genes”, with primary resistance to *ipilimumab*, a type of CTLA-4 inhibitor. Furthermore, the overexpression of these genes seem to be associated with epigenomic dysregulation, such as demethylation.

Additionally, the study could confirm that autophagy, a way of stimulating immunogenic cell death, was suppressed by elevated MAGE-A protein levels. There also seemed to be a correlation between dysregulation of autophagy and resistance to anti-CTLA-4 therapy, suggesting exploration of a synergistic therapeutic strategy.

One strength of the study is their use of several confirmatory evaluations which assessed the legitimacy of their findings. One example would be that they ensured that gender did not correlate with the clinical outcome, creditable since the genes were located on the X chromosome. However, one weakness of the study is the rather small cohort of 146 melanoma patients. The findings should probably be confirmed in another study with a larger population to improve the validity, although their findings seem promising.