Simposio Internacional: Estrategias de escape inmunológico del cáncer: implicaciones para la inmunoterapia
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NUMBERS AND FUNCTIONS OF T LYMPHOCYTES IN HUMAN MELANOMA METASTASES

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Phase I/II therapeutic vaccination trials in advanced melanoma patients have used tumor-specific antigens administered as peptides, proteins, dendritic cells pulsed with peptides, or recombinant poxviruses. Objective tumor regressions were observed in 10-20 % of the vaccinated patients, with a real clinical benefit in 6 %. T-cell response analyses indicated that the blood levels of anti-vaccine cytolytic T cells (CTL) were very low, even in patients displaying tumor regression. Detailed analysis of two patients showed that (i) tumor regression was associated with activation of CTL recognizing tumor-specific antigens absent from the vaccine, (ii) some of these CTL were already present before vaccination, (iii) new CTL appeared after vaccination: new clones against antigens that were already targeted prior to vaccination (clonal spreading), and new clones against antigens that were previously ignored (antigen spreading). The most likely explanation is that melanoma patients spontaneously mount anti-tumor CTL responses, which eventually become inefficient at rejecting the tumor ought to local immunosuppression or decreased antigen expression. Vaccination activates a few anti-vaccine CTL that upon arrival in the tumor relieve the suppression, sparking the activation of many more anti-tumor CTL, responsible for tumor regression.
We compared the gene expression profiles of pre-vaccine cutaneous metastases from melanoma patients who showed either complete tumor regression or no regression following vaccination with MAGE tumor antigens (MAGE-A3 peptides administered alone, or recombinant canarypoxviruses encoding MAGE-A1 and MAGE-A3 antigenic peptides). We observed no relevant difference between the two groups. But we noticed the presence of a specific inflammatory signature, quite variable between samples, and independent of the clinical evolution of the patients. It comprises T cell and macrophage markers. The T cell signature includes activation markers, IFNγ target genes, and the IFNG transcript itself. Using immunohistology on adjacent tumor sections, we established that this inflammatory signature correlates with the degree of immune cell infiltration in these tumors. Thus melanoma metastases host various degrees of active Th1 inflammation, and we conclude that the immunosuppressive environment in these tumors does not result in a complete inhibition of T cell activation.