DeMIM : DERMATOHELIOSIS, TUMOR MUTATION BURDEN AND IMMUNE RESPONSES IN MELANOMA PATIENTS

(L. BOUSSEMART)

In the last decade, the advent of immunotherapies with inhibitors of immune checkpoints known as "checkpoint inhibitors", including anti-PD-1 and anti-CTLA-4, has revolutionized the treatment of advanced or metastatic melanoma. However, the clinical benefit remains limited to a subset of patients. Identifying the patients most likely to benefit from these novel therapies is therefore critical. Previous studies found a significant link between the high tumor mutational burden (TMB) and response to anti-PD-1 monotherapy, regardless of the histological type of cancer. Unfortunately, TMB measurement is expensive, and requires Next Generation Sequencing (NGS) approaches difficult to implement in clinical practice. However, it has been observed that melanomas known to be secondary to mutagenic ultraviolet (UV) rays often carry on a high TMB. The cumulative UV damage translates into visible alterations on patients' skin, easy to recognize with the naked eye of the clinician around the scar of the primary melanoma. This project proposes to establish, for the first time, those skin alterations as a novel predictive factor of response to anti-PD-1 immunotherapy, to be used by dermatologists as a powerful decision-support tool to select the best treatment for an individual patient. Specifically, we will demonstrate the link between those alterations, TMB, immunogenicity and treatment response profiles through an extensive molecular characterization of the tumor DNA, histological analysis of the tumor tissues, frequency and reactivity of T cell subsets against melanoma antigens, and host immunological profiles of patients with strong *vs* weak pericicatricial alterations. This directly accessible, surrogate marker for TMB will be a game changer in clinical practice and will subsequently be translated to other skin cancers.