ABSTRACT

Ovarian cancer belongs to the gynecological malignancies with the worst prognosis, mainly due to the late diagnosis of this disease and limited therapeutic options for patients. Despite the undeniable progress in surgical and chemotherapy treatment, the mortality of this disease is still rather high. For this reason, several preclinical and clinical studies have been involved in identification of new treatment strategies (including immunotherapy) and characterization of new prognostic and predictive biomarkers to help determine the development of the clinical condition of patients or their response to treatment. The aim of this thesis was to better understand the role of the immune system in the tumor microenvironment (TME) of high-grade serous ovarian cancer (HGSC) and its possible prognostic role in the treatment of patients. Our results show that the presence of activated DC-LAMP$^+$ dendritic cells in the TME is associated with the induction of anti-tumor T helper type 1 response (Th1) and cytotoxic response. Surprisingly, the resulting effector activity of the cytotoxic T lymphocytes (CTLs) is not inhibited by the presence of programmed death-ligand 1 (PD-L1), programmed cell death (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and lymphocyte-activation gene 3 (LAG-3), as determined by genomic sequencing and immunohistochemical analysis in a large cohort of patients, but rather it is the result of a higher presence of the T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) molecule on CTLs. Our results clearly indicate that TIM-3 can serve as a negative prognostic biomarker associated with inhibition of anticancer immune response in HGSC patients. Our findings also show that the resulting activation of an antitumor immune response in TME is significantly influenced by the presence of danger associated molecular patterns (DAMPs). The high expression of calreticulin (CRT), the key molecule of DAMPs, in TME of patients correlates with higher effector activity of antitumor immune response and shows better prognosis of patients with HGSC. These results help to further understand the role of the immune system in the HGSC TME and identify possible prognostic biomarkers in the treatment of this serious disease.