IL17F-rs9463772 as an independent prognostic biomarker in locally advanced rectal cancer

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Immune system acts as a double-edged sword in different stages of cancer battle, exerting a direct activity both in the microenvironment and in the global response to cancer. The deeply definition of such mechanisms is essential to develop new strategies to harness the power of immunity to defeat cancer. A possible way to go in deepening this matter is to understand the potential role of polymorphisms (SNPs) in factors involved in immune system activity. One clinical setting of interest is represented by locally advanced rectal cancer (LARC). No prognostic biomarkers are available nowadays and the complexity of patients' management claims for further efforts. In addition, surrogate end-points of overall survival (OS) have been proposed, such as the 2-year disease free survival (2yDFS), even if they have not been introduced in the clinical practice yet.

This study aimed to identify new immunogenetic prognostic biomarkers in LARC patients who underwent multimodal therapy. The first clinical end-point was the identification of genetic biomarkers associated with the 2-year disease free survival (2yDFS). Their prognostic value were then tested with the 10-year OS (10yOS).

For this purpose, we selected 147 SNPs in 34 immune-related genes in a group of 235 LARC patients undergoing neoadjuvant therapy and surgery, and followed up for at least 24 months (training set). We analyzed this panel in a Veracode (Illumina) platform. Three prognostic biomarkers were significantly associated with both the 2yDFS and the 10yOS by multivariate COX regression and internally validated with bootstrap analysis, that are *IL17F*-rs641701, *IL17F*-rs9463772, and *STAT3*-rs8069645 (p=0.003, p=0.002, and p=0.044, respectively). Additionally, we performed the genetic analyses on a validation set of 63 LARC patients who underwent radical surgery and adjuvant treatment. The SNP *IL17F*-rs9463772 still resulted significant (p=0.045), highlighting its noteworthy prognostic role in this clinical model.

At the best of our knowledge, no functional data about the biological role of these SNPs are available nowadays. However, the obtained results are consistent with the literature data about the role exerted by IL17F and STAT3 in cancer setting.

The most important result is represented by the SNPs located on *IL17F*. This interleukin activates different signaling pathways, promoting the expression of proinflammatory cytokines such as TNF, IL1, and IL6. Intriguingly, IL17F is also involved in angiogenesis.

STAT3 is an oncogene activated by many inflammatory cytokines such as IL6. Its activation leads to cell proliferation, resistance to apoptosis, and angiogenesis, and its persistent activation characterizes different human malignancies. Its high tumour expression has been significantly associated with poor prognosis in CRC patients, suggesting the potential use of STAT3 as a new druggable target.

To better interpret our findings, we searched for a link between STAT3 and IL17F and, intriguingly, they are both involved in Th17 maturation and activity. The role of these immune cells in cancer is not well elucidated, even if there is a growing interest in its definition.

The obtained results are of interest due to the presence of the validation set, that shed light to the reliable prognostic role of *IL17F*-rs9463772. Functional analyses are needed to reinforce these results and to hopefully offer to clinicians new biomarkers to optimize LARC patients' management.