

Study finds major anti-inflammatory immune activity that favors oral cancer tumors

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Estefanía Nova-Lamperti, Ph.D.; from Universidad de Concepción, Mauricio Hernández, MSc and Prof. Elard Koch, Ph.D., from MELISA Institute. Credit: MELISA Institute

A collaborative research led by immunologist Estefania Nova-Lamperti from the Universidad de Concepción (Chile), with a branch of

researchers from MELISA Institute and other international academic centers, made progress in the understanding of molecular mechanisms preventing an effective antitumor immune response in oral cancer; The latter due to the production of chemical mediators that induce an anti-inflammatory regulatory response that favors tumor development through the vitamin D signaling pathway. The study was published in *Frontiers in Immunology* on May 7, 2021.

Oral cancer, 90% of which corresponds to the squamous cell type, is a neoplasm with a high mortality and morbidity rate, mainly because the diagnosis is made in late stages when metastases already exist, and where treatment produces serious physical and functional sequel among survivors.

It is well known that the immune system plays a key role in the development of cancer, either by stimulating pathways that play an anti-[tumor](#) role or, conversely, by generating an anti-inflammatory environment that allows the tumor to grow and be spread.

The main biological agents of the immune system are lymphocytes or T cells, which have different functions or phenotypes. In cancer, the presence of regulatory T cells (Tregs) and helper T cells type 2 (Th2) are associated with a worse prognosis, whereas the responses of helper T cells type 1 (Th1) within tumors, in general, show a better prognosis.

Dr. Nova-Lamperti points out that a key question in [oral cancer](#) is how an anti-inflammatory microenvironment is induced, boosting tumors growth. To date, "the immunoregulatory mechanisms associated with this change in the [immune response](#) are unknown and it is not acknowledged whether they come from or are external to the tumor," explains the immunologist.

Using flow cytometry techniques, the research team was able to feature

the T-cell phenotypes predominant in biopsies of 15 patients with oral cancer and compared them with the T-cell populations found in biopsies of 16 disease-free controls. Thus, they identified a predominant distribution of T cells expressing CCR8+ receptors (generally abundant in skin tissues), Th2-like regulatory T cells, and a small population of Th1 cells.

Based on these new findings, the researchers hypothesized that the tumor microenvironment obtained from biopsy cultures of patients with oral cancer, which contains the factors secreted by tumor cells (known as secretome), had the ability to induce an anti-inflammatory phenotype itself. To test this assumption, Nova-Lamperti and her colleagues challenged immune T cells subpopulations with the cancer secretome and, using genomics and proteomics techniques, determined how the mRNA transcripts and proteins expressed by these cells are modified.

Notably, transcriptomics showed that oral cancer secretome induced the expression of a group of genes that control the vitamin D (VitD) signaling pathway in T cells. Moreover, the proteomics study, through high-resolution mass spectrometry, revealed the presence of several proteins associated with the production of prostaglandin E2 (PGE2) linked to VitD rapid signaling in cell membranes. In addition, the researchers found a reduction in the proteins that carry VitD into the cell.

Based on these findings, the researchers suggested that the decrease in the mobility of VitD promotes an increase in its concentration in the tumor microenvironment, inducing an anti-inflammatory phenotype favorable to the tumor. In new experiments, the researchers challenged T-cell cultures with VitD and PEG2, confirming that VitD induces a Th2 regulatory response with expression of CCR8, while the combination of VitD and PEG2 inhibited the production of small proteins called cytokines. The latter are important for the activation of the immune

system. Additionally, the study showed that a cytokine that binds to the CCR8 receptor, known as chemokine CCL18, was overexpressed in tumors, favoring a vicious circle that stimulates the Tregs [cells](#) to 'stagnate' in the tumor microenvironment.

Regarding the effect of the study, the immunologist noted that "findings could be interesting for the development of biological therapies centered on antibodies capable of blocking the action of specific molecules that favor tumor growth. For example, in the case of oral [cancer](#), a therapy that selectively blocks the CCR8 receptor or that normalizes the vitamin D signaling pathway could eventually slow tumor growth, decrease the sequel of surgical resections, and improve survival in these patients." The researcher stressed the need to continue doing research in this regard.

Researcher Mauricio Hernández, a mass spectrometry expert at the MELISA Institute, stated that "collaborating in this research was challenging; the proteomics for this study required several time-consuming procedures to obtain optimal results. For example, because we dealt with cell culture media, each sample had to be depleted of abundant proteins such as albumin that 'shield' or make it difficult to detect smaller, less abundant proteins; then we performed an off-line fractionation to increase our identification capability. This encompasses a chromatography step to subdivide each sample, which substantially multiplies the number of runs on our mass spectrometer and increases the time in subsequent bioinformatic analysis."

Finally, Prof. Elard Koch, senior researcher and Chairman at the MELISA Institute, said that they were pleased to be invited to participate in the study led by Dr. Nova-Lamperti; "Collaborating with our multi omics capabilities in research as relevant as this one is encouraging for our researchers and a key goal for our institute" Koch remarked.

More information: Marco Fraga et al, Immunomodulation of T Helper Cells by Tumor Microenvironment in Oral Cancer Is Associated With CCR8 Expression and Rapid Membrane Vitamin D Signaling Pathway, *Frontiers in Immunology* (2021). [DOI: 10.3389/fimmu.2021.643298](https://doi.org/10.3389/fimmu.2021.643298)

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