DUTCH SOCIETY FOR IMMUNOLOGY

NVVI Van Bekkum thesis award 2018 goes to Fiamma Salerno

A balancing act: effective yet constrained T cell effector function

Tight regulation of cytokine production is essential for protective yet balanced T cell responses. Fiamma Salerno identified new post-transcriptional regulatory networks that enable T cells to produce the optimal amount of cytokines at the right time and place. Cytokines are essential for T cells to fight infected or tumor cells. These highly toxic molecules can also cause harm. "Understanding the fundamental biology that regulates cytokine production in T cells is key to identifying new therapeutic targets and to strengthen currently available immunotherapeutic approaches."

Fiamma Salerno's PhD thesis 'Walking the wire: Post-transcriptional regulation of T cell effector functions in health and disease' not only got her a cum laude doctorate. Her research in the group of Monika Wolkers at Sanquin was also awarded the NVVI Van Bekkum thesis award 2018. Salerno presently works as a post-doctoral researcher at the Babraham Institute in Cambridge (UK).

Discrepancy

Her thesis combines infection and tumor models with state-of-the-art RNA biology to study the regulation of cytokine production during *bona fide* T cell responses. "In our studies we combined the analysis of mRNA levels with protein output. This was key to dissect the regulatory processes that determine cytokine production in human and mouse primary T cells", Salerno says. "To produce any protein in our body, including cytokines, the information stored in our genome needs to be decoded. To this end, DNA is first transcribed into messenger RNA. This mRNA amplifies the information and serves as a blueprint to produce thousands of copies of proteins - cq cytokines. Although one would expect that mRNA molecules would directly lead to protein production, in reality, there is a discrepancy between mRNA and protein levels in about 50% of the cases."

Salerno found that memory T cells are 'pre-armed' with cytokine mRNAs. This 'pre-formed' mRNA is key for instantaneous response to infections. However, it is imperative that it remains silent until T cells encounter a target. Cytokine production without infection can be extremely harmful", Salerno explains. "The highlight of my thesis has been the identification of the brake that maintains and stalls 'pre-formed' cytokine mRNA in memory T cells".

Braking complex

Regulatory sequences presented within the mRNA, so-called AU-Rich Elements (ARE), can block cytokine production. Salerno: "ARE sequences are a hub for regulatory proteins to bind. We found that the RNA-binding protein ZFP36L2 can bind to AREs of cytokine mRNAs in memory T cells. When this occurs, ZFP36L2 prevents the mRNA to be recruited to the ribosome - the cell's 'protein production machinery'. ZFP36L2 binds cytokine mRNAs only in the absence of infection. Once T cells encounter infected cells, this blockade is lifted and cytokine production is immediately initiated without losing time to first amplify the DNA."

Interestingly, Salerno found that AREs do not only mediate a brake against unwanted cytokine production, but also define the levels and the duration of cytokine production upon infection. "ARE-mediated regulation fine-tunes cytokine production, as it guarantees optimal fighting against infection and cessation once the infection is resolved."

Therapeutic window

"Discrepancy between mRNA and protein levels is not only found in physiology" Salerno continues. "In case of cancer or chronic infection with HIV or Hepatitis C, T cells gradually loose their ability to produce

cytokines, and thus to kill tumor cells or infected cells. Despite their inability to produce cytokines, we observed that T cells in a tumor still contain cytokine mRNA. Again, ARE-mediated regulation is responsible for this block of cytokine production".
In a pre-clinical mouse model of melanoma, Salerno demonstrated that cytokine production could be restored by simply removing AREs from the cytokine mRNA. "By prolonging cytokine production of tumor-infiltrating T cells we can improve their efficacy to block tumor growth."
She indicates that AREs could be new potential therapeutic targets: "Similar strategies could be used in human T cells to make anti-cancer immunotherapy more efficient."
Salerno now continues her studies of RNA biology and immunology in Cambridge. "My next challenge is to understand how signal strength and signal transduction regulates the activity of RNA-binding proteins in B cell fate decision and long-lasting immunity. I hope that my research will continue advancing our basic understanding of gene regulation and may help underpinning new mechanistic insights to improve health and optimize vaccine designs."

Leendert van der Ent
Bureau Loriënt