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T cell memory in Capri

A successful course organized by the EFIS-EJI Ruggero Ceppellini Advanced School of Immunology founded by Serafino Zappacosta

Capri, queen of rock, as Pablo Neruda defined it, is the Italian island that hosted the "EFIS-EJI Ruggero Ceppellini School course on T cell memory" from October 12 to 15, 2018. Since its foundation by Serafino Zappacosta, Antonio Di Giacomo et al in 1991, the EFIS-EJI Ruggero Ceppellini School was aimed to promote in-depth immunology studies both at national and international level, and to encourage international exchanges also by supporting participants from developing countries. The aim of the 2018 Course was to give an overview and discuss open questions about development, maintenance, and function of memory T cells. The Course Scientific Directors were Francesca Di Rosa (Institute of Molecular Biology and Pathology, Italian National Research Council, CNR, Rome, Italy) and Stephen P. Schoenberger (La Jolla Institute for Allergy and Immunology, California, USA), and the Course venue was the "Osservatorio Cultura Ricerca Formazione Divulgazione", a Congress Center owned by the CNR in Anacapri village (Capri island, Naples, Italy).

In her opening keynote lecture Polly Matzinger (National Institutes of Health, MD, USA) (fig. 1) started by asking to the audience the following hot question: "How does the immune response starts?". She then discussed the answer offered by the Danger Theory, proposing that tissue damage and release of alarm signals from injured cells trigger the immune system [1]. What we considered so far innocuous "self" can be dangerous in certain conditions and thus able to trigger immune response. In her closing keynote lecture, Matzinger provided examples of how autoimmunity and tumors can be examined from the point of view of the Danger Theory. For example, in some autoimmune diseases there might be nothing wrong with the immune system itself, but rather something wrong with the target tissue and its release of alarm signals.

The resident memory T cell (TRM) subset was the topic of David Masopust's lecture (University of Minnesota, MN, USA). Although some classical TRM markers are useful to identify CD8 Tissue-Resident Memory cells (TRMs) in non-lymphoid tissues (such as CD103 and CD69), these cells

Figure 1. Keynote lecture by Polly Matzinger at the T cell memory course in Anacapri. © FuoriRotta srl.

can acquire different phenotypes and functions depending on the tissues in which they reside. Furthermore flow cytometry analysis of lymphocytes from non-lymphoid tissues has some limitations, for example only a tiny proportion of cells are recovered, and they might not fully represent the whole population in the tissue. For these reasons microscopy and transcriptional analysis should be preferred for CD8 TRM evaluation [2]. TRMs might also play important roles in tumor immune-surveillance. This concept was extensively discussed by Renè Van Lier (Sanquin Blood Supply Foundation, Amsterdam, NL), who focused on the analysis of TRMs in human lung tumors and on molecular regulation of TRM differentiation, and by Andrew D. Weinberg (Earle A. Chiles Research Institute, Portland, OR, USA), who discussed his recent findings on tumor-infiltrating CD8 T cells (CD8 TIL) co-expressing CD39 and CD103 [3]. These cells, which have a TRM phenotype and express high levels of exhaustion markers, contain a high frequency of functional tumor-reactive cells and have a distinct TCR repertoire.

The maintenance of immunological memory in the bone marrow was discussed by Francesca Di Rosa, who gave an overview of previous findings on bone marrow T cells and explained her recent "two-niches" hypothesis [4]. She discussed how bone marrow niches might regulate the cell cycle of memory T cells according to her hypothesis, and thus support either the stability of recirculating CD8 T cell numbers over time or the capacity to promptly mount a secondary response upon challenge. She also reported new findings on the kinetics of cell cycle of antigen-specific memory CD8 T cells in a mouse model of intramuscular vaccination with recombinant viral vectors [5]. Stephen Schoenberger opened his lecture with an overview of induction and modulation of T cell responses against infections and tumors, and discussed in depth the role of $CD4^+$ 'helper' T cells in regulating the response of $CD8^+$ 'killer' T cells. He presented his new findings showing that $CD4^+$ T cells help $CD8^+$ T cells via CD40-CD40L signaling at low infectious doses, while at high infection doses there is a rapid conversion of CD4 T cells to phenotypic and functional $Foxp3^+$ $CD25^+$ T regulatory cells.

Epigenetic regulation during memory T cell differentiation was the topic discussed by Luigia Pace (Italian Institute for Genomic Medicine, Turin, IT). She highlighted that the histone methyltransferase Suv39h1 regulates the acquisition of stem-like features and the terminal differentiation of memory CD8 T cells [6]. The emerging scenario is that epigenetic regulation can be exploited for the manipulation of T lymphocyte responses, in the context of vaccination and T cell-based immunotherapies. These concepts were further discussed by Peter D. Katsikis (Erasmus University, Rotterdam, NL), who focused his attention on the post-transcriptional regulation of normal $CD8^+$ T cell differentiation, and on its dysfunction in chronic infections and cancer, emphasizing the role of microRNAs in T cell responses. Vincenzo Barnaba (Sapienza University, Rome, IT) discussed human $CD8^+$ T cells responses against apoptotic self-epitopes in tumor and autoimmune diseases, and how he envisions their involvement in disease immunopathology. He then proposed to exploit measurement of apoptotic self-epitopes-reactive $CD8^+$ T cells in blood to predict responsiveness of rheumatoid arthritis patients to tumor necrosis factor-α inhibitor therapy.

Figure 2. Lecture by Dietmar Zehn chaired by the course co-director Stephen Schoenberger. © FuoriRotta srl.

A small subpopulation of virus-specific $CD8^+$ T cells that sustain T cell responses during chronic infections was described by Dietmar Zehn (The Technical University of Munich, Freising, Germany) (fig. 2).

Figure 3. Best poster presentation award: from left to right the 4 best poster presenters (Jonas Mackerodt, Miguel Munoz-Ruiz, Donald Nyangahu and Leen Hermans), the course co-director Francesca Di Rosa and the sponsor Sara Sampietro (Biolegend). © FuoriRotta srl.

These cells were defined by the expression of the transcription factor Tcf1 and shared key characteristics of central memory cells. Unlike conventional memory cells, Tcf1-expressing T cells displayed hallmarks of an "exhausted" phenotype, including the expression of inhibitory receptors such as PD-1. Thus, this subset might be a prime target for therapeutic interventions to improve the immune response in chronic infections [7].

In agreement with the principles of The Ceppellini School, the faculty of T cell memory course encouraged a constructive interaction among participants, both during talks (interruptions to ask urgent questions were always welcome!) and in the coffee/lunch breaks. Students were very active in asking questions during speaker talks, and they presented and discussed their own data during the two poster sessions in the afternoon. The four best poster presenters were selected to compete for the best poster presentation award, and were given the opportunity to present a short talk during the last session. They were Jonas Mackerodt (Imperial College, London, UK), Miguel Munoz-Ruiz (Francis Crick Institute, London, UK), Leen Hermans (Ghent University, Belgium) and Donald Nyangahu (Seattle Children's Research Institute, USA). Miguel Munoz-Ruiz won the first prize by giving an excellent presentation on his new data obtained in Adrian Hayday's lab on T cell regulatory networks in murine allergic contact dermatitis (ACD). He discussed his model proposing that skin CD8 TRM activity is regulated by γδ T cells through PD-L1/PD1 mediated interaction (fig. 3).

Both the scientific program and the schedule of the Course were carefully planned, so that there was also time for extra activities such as the excursion to the Damecuta archaeological site in Anacapri and the social dinner, that brilliantly completed this learning experience, in the wonderful context of Capri island.

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