REPORT
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STUDY AND TRANSLATIONAL IMPLICATIONS OF IMMUNE EVASION IN CHRONIC LYMPHATIC LEUKEMIA

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1. Summary

Chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in adults in our country. Patients with CLL are mainly diagnosed at early asymptomatic stages, while in about half of the patients the disease will eventually progress, and treatment will be needed. The mechanisms underlying progression are not fully elucidated and the identification of patients with higher probability of short time to progression is still a challenge. Preliminary longitudinal studies carried out by our group indicate that progression in CLL is characterized by a progressive dysfunction of the immune system. The deletion of chromosome 13q14, the most common genetic alteration in CLL, induces the development of CLL in animal models with relatively low penetrance, which could be explained by leukemic control by T lymphocytes. Based on these data our goal is to decode the immunological mechanisms involved in CLL progression and to transfer this information into a better prognostication and treatment selection. The specific objectives of the present project are firstly to longitudinally study the co-evolution of CLL and the immune system from early stage CLL to clinical progression. The second objective is to study the immune evasion and immunomodulation in the development of CLL in a mouse model of CLL with incomplete penetrance, and to ascertain the role of immunomodulatory drugs in the reversion of these mechanisms. Methodology: we will study genome-wide expression changes in both CLL and immune system cells by means of gene-wide gene-expression analysis and multiparametric spectral flow cytometry. We will also study immunological characteristics in mice with 13q14 deletion according to the development of CLL and will test immunomodulatory therapies that can potentially impede CLL progression. Finally, the absolute increase in immune dysfunction will be computed and combined with other prognostic factors, to build an algorithm to predict time to progression.

2. Results

During the development of the project we have set up a system to thoroughly assess the immunocompetence of the adaptive immune system in patients with CLL. We have quantified the dynamic immunological changes that precede clinical progression. This progressive immunosuppression not only favours clinical progression of the leukemia but is also potentially useful to predict which patients are most likely to experience

rapid clinical progression and thus are in need of treatment. These observations are currently being validated in an independent cohort of patients. Regarding the mouse model, we have observed how the progressive deterioration of the immune system precedes the development of CLL. We are currently testing different therapeutic interventions that can potentially impede such immunosuppression and, therefore, impede the full development of CLL, even in the presence of causative genetic defects in mature B lymphocytes. The final analysis of the results will ultimately help better define prognosis of patients while thoroughly studying the mechanisms of progression in CLL and studying the role of early immunomodulating treatment in CLL.

3. Relevance and potential future clinical implications

This project holds significant relevance and potential clinical applicability in the field of CLL research and treatment. The early identification of patients that will experience an early progression through the development of advanced prognostic scores is undoubtedly of interest for both researchers and clinicians interested in CLL.
This project aims to decode the immunological mechanisms involved in CLL progression. Given that CLL is often diagnosed at early asymptomatic stages and progresses differently among patients, understanding the underlying mechanisms of progression is crucial. By studying the co-evolution of CLL and the immune system longitudinally, the project addresses a gap in current knowledge regarding the dynamics of CLL progression.

The development of an immunoscore, which combines these markers with other prognostic factors, could lead to a more accurate prediction of time to progression for individual patients. This prognostic tool could help clinicians stratify patients based on their risk of progression and tailor treatment plans accordingly.

Investigating immunomodulatory therapies in a mouse model of CLL with incomplete penetrance provides insights into potential interventions to impede CLL progression. Understanding how these therapies affect immune evasion and immunomodulation in CLL development could pave the way for the development of novel treatment approaches aimed at targeting the immune dysregulation characteristic of CLL progression.

Finally, the project's two-phase approach, involving discovery and validation of the immunoscore in independent cohorts, enhances the robustness and generalizability of the findings. If successful, the immunoscore could serve as a clinically relevant tool for prognostication and treatment selection in CLL patients, ultimately improving patient outcomes.

In summary, this project addresses key gaps in our understanding of CLL progression mechanisms, holds promise for the development of prognostic tools, and offers insights into potential immunomodulatory treatment strategies. If successful, the findings could have significant clinical implications for the management of CLL patients, ultimately improving outcomes and quality of life.

4. Scientific publications

Research papers

1. Isabel Jiménez, et al., Immunological and genetic kinetics from diagnosis to clinical progression in chronic lymphocytic leukemia. Biomarkers Research, 2021 May 20;9(1):37. Doi: 10.1186/s40364-021-00290-z.

2. Pau Abrisqueta et al., A gene expression assay based on chronic lymphocytic leukemia activation in the microenvironment to predict progression. Blood Adv. 2022 Aug 16;bloodadvances.2022007508

3. Daniel Medina et al., Multi-omics exploration of microenvironmental changes during BTK covalent inhibition in chronic lymphocytic leukemia. Under review.

Meeting communications

1. Daniel Medina, Laura Palomo, Víctor Navarro, Oriol Castells, Belén Sánchez, Pau Marc Muñoz Torres, Carlota Pagès Geli, Cristina Hernández, Gemma Pujadas, Christelle Ferrà, Miguel Alcoceba, María José Terol, Rafael Andreu, Francesc Bosch, Pau Abrisqueta, Marta Crespo, Immune-profiling of ibrutinib-treated CLL patients revealed TMBIM6 as a potential target for CLL and its high expression as an independent variable associated with poor prognosis. XX International Workshop on Chronic Lymphocytic Leukemia 2023

2. Daniel Medina, Laura Palomo, Víctor Navarro, Oriol Castells, Belén Sánchez, Pau Marc Muñoz Torres, Carlota Pagès, Cristina Hernández, Gemma Pujadas, Christelle Ferrà, Miguel Alcoceba, María José Terol, Rafael Andreu, Francesc Bosch, Pau Abrisqueta, Marta Crespo. Multi-omics exploration of adaptive mechanism to BTK inhibition identified TMBIM6/BI-1 as a poor prognosis variable and potential target for CLL. The American Society of Hematology - 65th Annual Meeting and Exposition

3. Daniel Medina, Laura Palomo, Víctor Navarro, Beatriz Martín-Mur, Oriol Castells, Belén Sánchez, Pau Marc Muñoz Torres, Carlota Pagès, Cristina Hernández, Gemma Pujadas, Anna Esteve-Codina, Alba Cabirta, Christelle Ferrà, Miguel Alcoceba, María José Terol, Rafael Andreu, Pau Abrisqueta, Francesc Bosch, Marta Crespo. Exploración multiómica de los cambios en el microambiente tumoral durante la inhibición covalente de BTK en la leucemia linfocítica crónica. 14ª Reunión GELLC.