Dissecting the cellular and molecular dynamics of bone marrow fibrosis for improved diagnostics and treatment

Informe

Información del proyecto

deFIBER

Identificador del acuerdo de subvención:
757339

DOI
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Proyecto cerrado

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Coordinado por
ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM
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Periodic Reporting for period 3 - deFIBER (Dissecting the cellular and molecular dynamics of bone marrow fibrosis for improved diagnostics and treatment)

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Resumen del contexto y de los objetivos generales del proyecto

Fibrosis is the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections, autoimmune reactions, chemical insults, radiation, tissue injury and importantly cancer. Fibrosis is often a life-limiting condition as it significantly reduces the organ function or in case of the bone marrow, the blood production. Established fibrosis is non-reversible. Thus, the progression of fibrosis needs to be halted in an early stage. Myelofibrosis (MF) is an incurable blood cancer and the prototypic example of progressive development of bone marrow fibrosis. The bone marrow morphology in patients with MF suggests that there is a stepwise evolution from an initial pre-fibrotic phase to a fibrotic phase. However, the initial changes in the pre-fibrotic phase are not well understood and no specific markers for the early diagnosis have been defined. One major shortcoming is that specific anti-fibrotic therapies related to blood cancer do not exist. The only potentially curative option is an allogeneic stem cell transplant (ASCT). However, the majority of patients is not eligible for this high-risk procedure and the outcome is unpredictable. So far, all FDA approved therapeutic strategies focus on eliminating the malignant hematopoietic clone but not on the actual fibrosis-driving cells and pro-fibrotic stimuli. We identified disease-specific mechanisms in the fibrosis-driving cells as protagonists of fibrosis.
We demonstrated that fibrosis-driving cells are the long-sought biomarker and therapeutic target in bone marrow fibrosis related to. blood cancer. We believe that predictive biomarkers which at the same time act as therapeutic targets are the unmet need in the diagnosis and treatment of fibrosis related to blood cancer.

Trabajo realizado desde el comienzo del proyecto hasta el final del período abarcado por el informe y los principales resultados hasta la fecha

We have applied state-of-the-art techniques, including genetic fate tracing experiments, conditional genetic knockout mouse models, single cell RNA sequencing and in vivo and in vitro CRISPR/Cas9 gene editing, to unravel the complex molecular and cellular interaction between fibrosis-causing cells and the malignant hematopoietic cells in MPN. We now translate our findings into patient samples with the aim to improve the early diagnosis of the disease and to ultimately develop novel targeted therapies with curative intentions.

Avances que van más allá del estado de la técnica e impacto potencial esperado (incluida la repercusión socioeconómica y las implicaciones sociales más amplias del proyecto hasta la fecha)

We identified a player of the innate immune system as a prognostic and predictive biomarker and importantly showed that targeting with a small molecular inhibitor reduced bone marrow fibrosis but also the cancer cell burden in MPN, in the sense of a targetable biomarker. We plan to move these findings from a pre-clinical to a clinical setting, including preparation of clinical studies.

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