A new therapy for the treatment of myeloproliferative diseases

Summary:

Myelodysplastic/myeloproliferative neoplasms (MPN) are a group of diseases that affect normal blood cell production in the bone marrow. In this case the bone marrow causes an overproduction of one or more blood cell types (red cells, white cells or platelets). Complications arise over time due to the abnormally high number of blood cells that accumulate in the bone marrow and in the circulating blood. In many cases, these diseases develop slowly and get worse gradually. In some cases, MPN can progress to leukemia. Compounds capable of preventing and treating these types of diseases are urgently needed.

CNIC researchers have identified new therapeutic targets based on alterations in the regulation of mesenchymal stem cells (MSC) in the hematopoietic niche by sympathetic nerves. They have also defined an *in vitro* method for prognosis/diagnosis of MPNs and/or to define the disease´s stage, and a method to *screen* for therapeutic compounds useful to treat MPNs.

Innovative aspects:

CNIC researchers have described the neural mechanisms regulating the hematopoietic niche, regulatory mechanisms that are impaired in myeloproliferative neoplasms and that contribute to the disease´s pathogenesis, thereby emerging as new therapeutic targets. They have demonstrated that production of Interleukin-1 beta by mutant progenitors can damage the Schwann cells that protect sympathetic nerve endings in the bone marrow. This neuro-glial damage enhances the susceptibility of mesenchymal stem cell in the hematopoietic niche to cell death caused by mutant hematopoietic cells.

They have showed that CXCL12, a chemokine produced by nestin MSCs, can partially control the expansion of the mutant hematopoietic progenitors. The decrease in MSCs in the bone marrow and the concomitant decrease in CXCL12 levels in MPN accelerates disease progression. The use of neurotrophic agents that prevent or rescue neuro-glial damage, together with beta3-adrenergic agonists, which make up for the deficit of sympathetic stimulation of nestin MSCs, can control the expansion of leukemic stem cells and arrest disease progression.

Therefore, they have proved the existence of a sympathetic neuropathy in MPN affecting the hematopoietic niche in the bone marrow, which plays an essential role in MPN pathogenesis

and has consequently emerges as a new therapeutic target.

Competitive advantages:

- This development could lead to the design of more efficient therapies for MPN treatment using currently available drugs, alone or in combination with other available treatments.

- We define a new MPN treatment that can arrest disease progression. This treatment could be extended to other hematological disorders that involve the degeneration of sympathetic fibers innervating the bone marrow.

Key words: myeloproliferative neoplasms, hematopoietic niche, bone marrow neuropathy, sympathetic fibers.

Technology type: Diagnosis, myeloproliferative neoplasms, therapeutics.

Patent information: EP2994119A1 (pending), US10335380B2 (granted) and JP6479818B2 (granted).

Stage of development: phase 2 study SAKK 33/14 compledted.

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