ANTIBODIES FOR USE IN THE PROPHYLACTIC AND/OR TREATMENT OF BACTERIAL INFECTIONS, CANCER METASTASIS AND ALZHEIMER DISEASE.

Summary:

Patrolling monocytes (PMo) have been reported to have a crucial function in acute pathological processes such as tumor metastasis, bacterial infections and autoimmune diseases. Although it has been proposed that a better function of these monocytes could be beneficial in these diseases, until now, no procedure has been identified to promote such function. CNIC researchers have discovered that the absence of MT4-MMP protease in patrolling monocytes increases their surface level of the alphaMbeta2 integrin receptor, which in turn increases its patrol function. Therefore, researchers propose to improve the patrolling monocytes' activity using antibodies anti MT4-MMP. This increased activity may offer a new therapeutic strategy for acute pathological processes.

Innovative aspects:

Patrolling monocytes, a type of white blood cell, exhibit unique functions in the vasculature in homeostasis and in inflammatory disease. Classical monocytes can migrate into damaged and infected tissues where they differentiate into inflammatory macrophages, whereas patrolling monocytes have been reported in several disease settings to survey the endothelium and remove damaged cells and debris from the vasculature, having been associated with wound healing and the resolution of inflammation in injured tissues. Patrolling monocytes (PMo) exert their surveillance activity within the vasculature, where they recognize endothelial damage and promote repair. Crawling of PMo on the inflamed endothelium has been reported to be dependent on αMβ2 integrin.

The matrix metalloproteinases (MMPs) are enzymes involved in the processes of tumor growth, invasion (direct extension and penetration by cancer cells into neighbouring tissues) and metastasis. They are frequently overexpressed in malignant tumors. Membrane-type 4 matrix metalloproteinase (MT4-MMP) is anchored to the plasma membrane and it has been suggested to promote breast cancer metastasis and glial cancers (a general term for numerous tumors of the central nervous system). MT4-MMP can cleave αM integrin (Itgam) and its absence leads to enhanced αM integrin-dependent crawling of patrolling monocytes. CNIC researchers have shown for the first time that the absence or deficiency of MT4-MMP proteolytic activity enhances the levels of αM integrin receptor, which in turn increases the activity of patrolling monocytes. Also for the first time, the inventors disclose MT4-MMP-mediated cleavage of αM integrin (Itgam) as a mechanism for regulating PMo crawling and extravasation to the target tissue.

CNIC researchers have demonstrated in a MMP knock out mouse model that the absence of this specific MMP increases bacterial clearance and improves survival

against a systemic infection by Listeria monocytogenes. In addition, in vivo data showed that the absence of MMP in monocytes results in a significant reduction of the number of lung melanoma metastasis.

CNIC researchers propose that MT4-MMP inhibition might offer a new therapeutic strategy for the treatment of those diseases wherein an improvement of the activity of patrolling monocytes would be beneficial, such as bacterial infections, cancer metastasis and Alzheimer disease. Non-specific inhibitors such as TIMP1 can reduce the activity of MT4-MMP. However, CNIC researchers propose its specific inhibition by antibodies directed against its catalytic domain. They have studied some anti MT4-MMP antibodies that showed to be specific, to bind to the native protein and to have MT4-MMP inhibitory activity. Finally, they selected the monoclonal antibody LEM-3/10, which recognized the native human and mouse MT4-MMP.

Competitive advantages:

- Non-specific inhibitors can reduce the activity of MT4-MMP, but CNIC researchers propose its selective inhibition by antibodies directed against its catalytic domain.
- The monoclonal antibody LEM-3/10 has very specific reactivity against the native protein and has MMP inhibitory activity.
- MT4-MMP inhibition may offer a new therapeutic strategy for acute pathological processes, wherein an improvement of the activity of patrolling monocytes would be beneficial. This improvement will promote:
  - A better fight against circulating metastatic cells, particularly to the lung.
  - A better fight against bacterial and virus infectious agents.
  - A decrease of deposits in cerebral amyloid angiopathy in Alzheimer's disease.

Key words: patrolling monocytes, bacterial infections, Alzheimer's disease, cancer metastasis, matrix metalloproteinase, MMP, MT4-MMP, αM integrin, antibodies, anti MT4-MMP, monoclonal antibody LEM-3/10.

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Stage of development: in vitro and in vivo studies

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