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Antibodies for the treatment of infections, tumor metastasis and Alzheimer disease.

Summary:

The present invention refers to the field of medicine and immunology. Specifically it relates to inhibitors of a matrix metalloproteinase (MMP) for use in the prophylactic and/or therapeutic treatment of diseases benefiting from an increase in the activity of patrolling monocytes (PMo), such as infections (e.g. *L. monocytogenes* infection), neurological diseases (e.g. Alzheimer's disease) and cancer. It further relates to said MMP inhibitors binding to particular amino acid sequences and epitopes within the MMP.

Innovative aspects:

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 a family of zinc-binding endopeptidases involved in the degradation of the extracellular matrix and are collectively responsible for tissue remodeling during embryogenesis, organogenesis, tissue regeneration, wound healing and many other physiologic and pathologic conditions, such as malignant tumors.

The inventors have shown for the first time that the absence or deficiency of a specific MMP proteolytic activity enhances the levels of αMβ2 integrin receptor, which in turn increases the activity of patrolling monocytes.

On the basis of the obtained results the inventors proposed that said MMP inhibition offers a new therapeutic strategy, for the treatment of those diseases wherein an improvement of the activity of patrolling monocytes would be beneficial.

The inventors 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*. Also *in vivo* data are presented showing that absence of the said MMP in monocytes results in a significant reduction of the number of lung melanoma metastasis.

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Competitive advantages:

For the first time, the inventors disclose this MMP-mediated cleavage of αM integrin as a mechanism for regulating patrolling monocyte (PMo) crawling and extravasation to the target tissue. The present invention thus discloses PMo as a new cellular target of specific MMP inhibitors and the hindering of the metastatic process through reduction/inhibition of the MMP activity in monocytes is therefore considered to be a new therapeutic effect providing a new medical situation.

In addition, a series of monoclonal antibodies were obtained by mouse immunization. The binding and functional characteristics of these antibodies are shown in the invention. Various of these anti-MMP antibodies were shown to be specific, to bind to the native protein and to have the MMP inhibitory activity.

Moreover, the invention provides the *in silico* identification of putative epitopes within the MMP, wherein binding thereto is expected to result in inhibition of the MMP catalytic activity.

Key words: matrix metalloproteinase, MMP**,** MMP inhibitors, antibodies, Ab, patrolling monocytes, infections, Alzheimer's disease, cancer.

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