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Metalloproteinase MT1-MMP islets act as memory devices for podosome reemergence

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ABSTRACT:

Podosomes are dynamic cell adhesions that are also sites of extracellular matrix degradation, through recruitment of matrix-lytic enzymes, particularly of matrix metalloproteinases. Using TIRF microscopy, we show that the membrane-bound metalloproteinase MT1-MMP is enriched not only at podosomes, but also at distinct “islets” embedded in the plasma membrane of primary human macrophages. MT1-MMP islets become apparent upon podosome dissolution and persist beyond podosome lifetime. Importantly, the majority of MT1-MMP islets are reused as sites of podosome re-emergence. SiRNA-mediated knockdown and recomplementation analyses show that islet formation is based on the cytoplasmic tail of MT1-MMP and its ability to bind the subcortical actin cytoskeleton. Collectively, our data reveal a previously unrecognized phase in the podosome life cycle and identify a structural function of MT1-MMP that is independent of its proteolytic activity. MT1-MMP islets thus act as cellular memory devices that enable efficient and localized reformation of podosomes, ensuring coordinated matrix degradation and invasion.

STATEMENT:

Our data show that the matrix metalloproteinase MT1-MMP, a master regulator of proteolytic cell invasion, plays crucial roles not only at the endpoint of podosome assembly, by enabling degradation of extracellular matrix material, but also by functioning as a subcellular signpost that facilitates formation of new podosomes at sites of previously disassembled structures. These findings reveal a novel structural function of MT1-MMP that is independent of its proteolytic activity. At the same time, our study has high translational potential, as it also provides a new concept for the study of other adhesion and invasion structures, most notably invadopodia, and their contribution to cell invasion and cancer progression.

The manuscript has the cover and is the title story of the respective issue of JCB.

BACKGROUND:

This work was performed at the Institute for Medical Microbiology, Virology and Hygiene in the group of Stefan Linder, who holds a professorship at UKE since 2009. It was part of the PhD thesis of Karim El Azzouzi. The authors have strong research interests in the field of cytoskeletal regulation and intracellular trafficking, with a special focus on macrophage biology and pathophysiology.