Sociedad Argentina de Microbiología General

XIX CONGRESO DE LA SOCIEDAD ARGENTINA DE MICROBIOLOGÍA GENERAL

22 al 25 de octubre del 2024
Centro cultural y Pabellón Argentina de la Universidad Nacional de Córdoba, Córdoba, ARGENTINA.

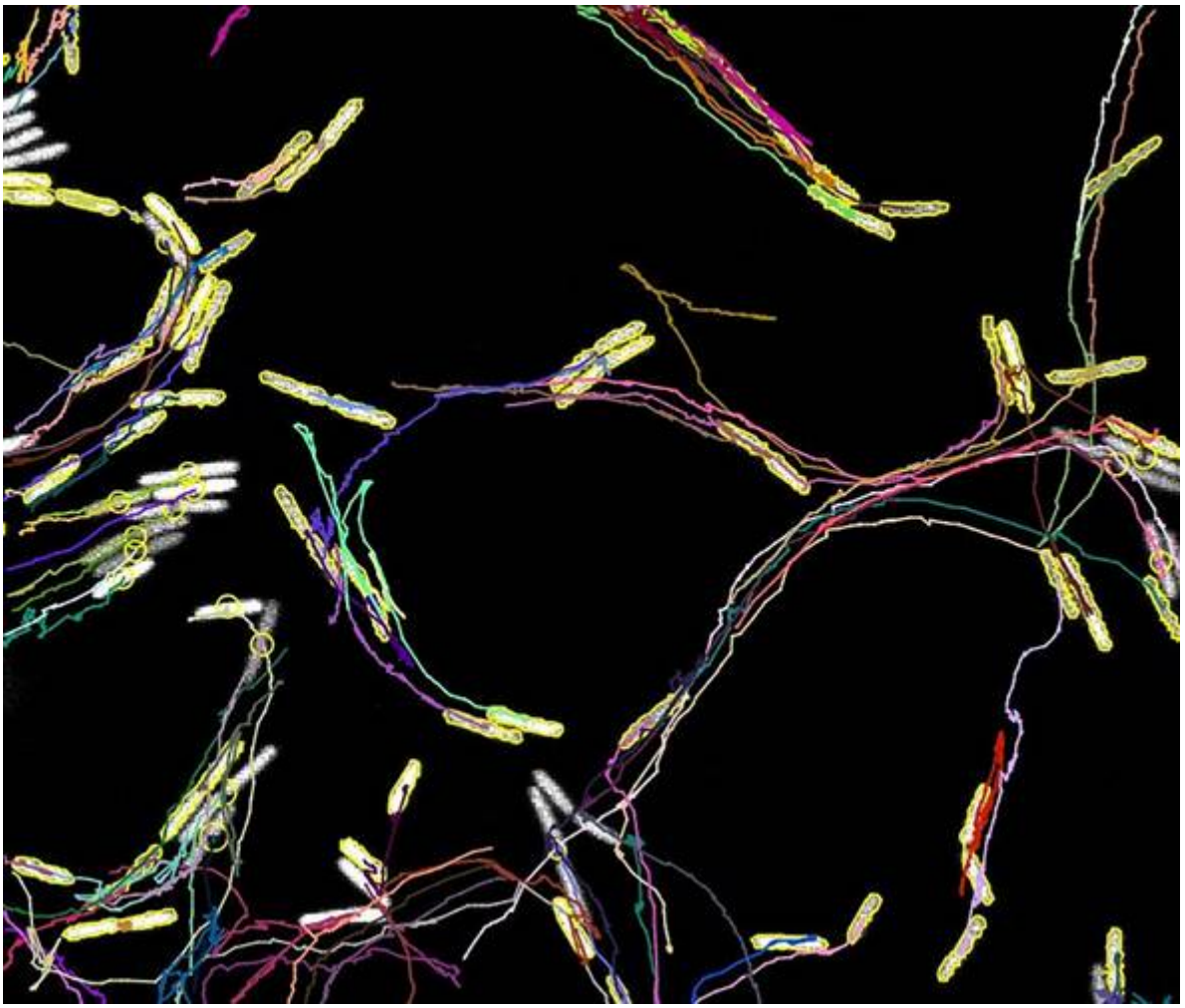

Foto: Se hace camino al andar. Celeste Dea. 1er puesto. Concurso fotográfico SAMIGE 20 años.

230 - invitados

CRACKING THE CODE OF PROTEIN STABILITY IN THE PERIPLASM: ANOTHER BRICK IN THE RESISTANCE WALL

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Protein stability is an essential property for biological function. In contrast to the vast knowledge on protein stability in vitro, little is known about the factors governing in-cell stability. Here we show that the metallo-?-lactamase (MBL) NDM-1 is a kinetically unstable protein upon metal restriction that has evolved by acquiring different biochemical traits that optimize its in-cell stability. The host native immune system response limits the availability of the Zn(II) ions at the infection sites through the secretion of the metal scavenging protein Calprotectin, leading to accumulation of the non-metalated (apo) NDM-1 variant in the periplasm, that is degraded by the periplasmic protease Prc by recognition of a partially unstructured C-terminal domain. Accumulation of misfolded apoNDM-1 is further targeted by the canonical housekeeping protease DegP. The non-metalated (apo) NDM-1 is degraded by the periplasmic protease Prc that recognizes its partially unstructured C-terminal domain. Zn(II) binding renders the protein refractory to degradation by quenching the flexibility of this region. Membrane anchoring makes apo-NDM-1 less accessible to Prc and protects it from DegP, a cellular protease degrading misfolded, non-metalated NDM-1 precursors. NDM variants accumulate substitutions at the C-terminus that quench its flexibility, enhancing their kinetic stability and bypassing proteolysis. These observations link MBL-mediated resistance with the essential periplasmic metabolism, highlighting the importance of cellular protein homeostasis.
We also studied the degradation of apo-NDM-1 in the periplasm of E. coli by in-cell NMR. We identified the cleavage sites of each protease and their concerted mechanism of action providing new insights about the molecular recognition events in living E. coli cells. Our initiative highlights the potential of in-cell NMR to characterize molecular networks within the cell, in a highly challenging subcellular compartment such as the bacterial periplasm.

Palabras clave: palabras_clave