Sociedad Argentina de Microbiología General

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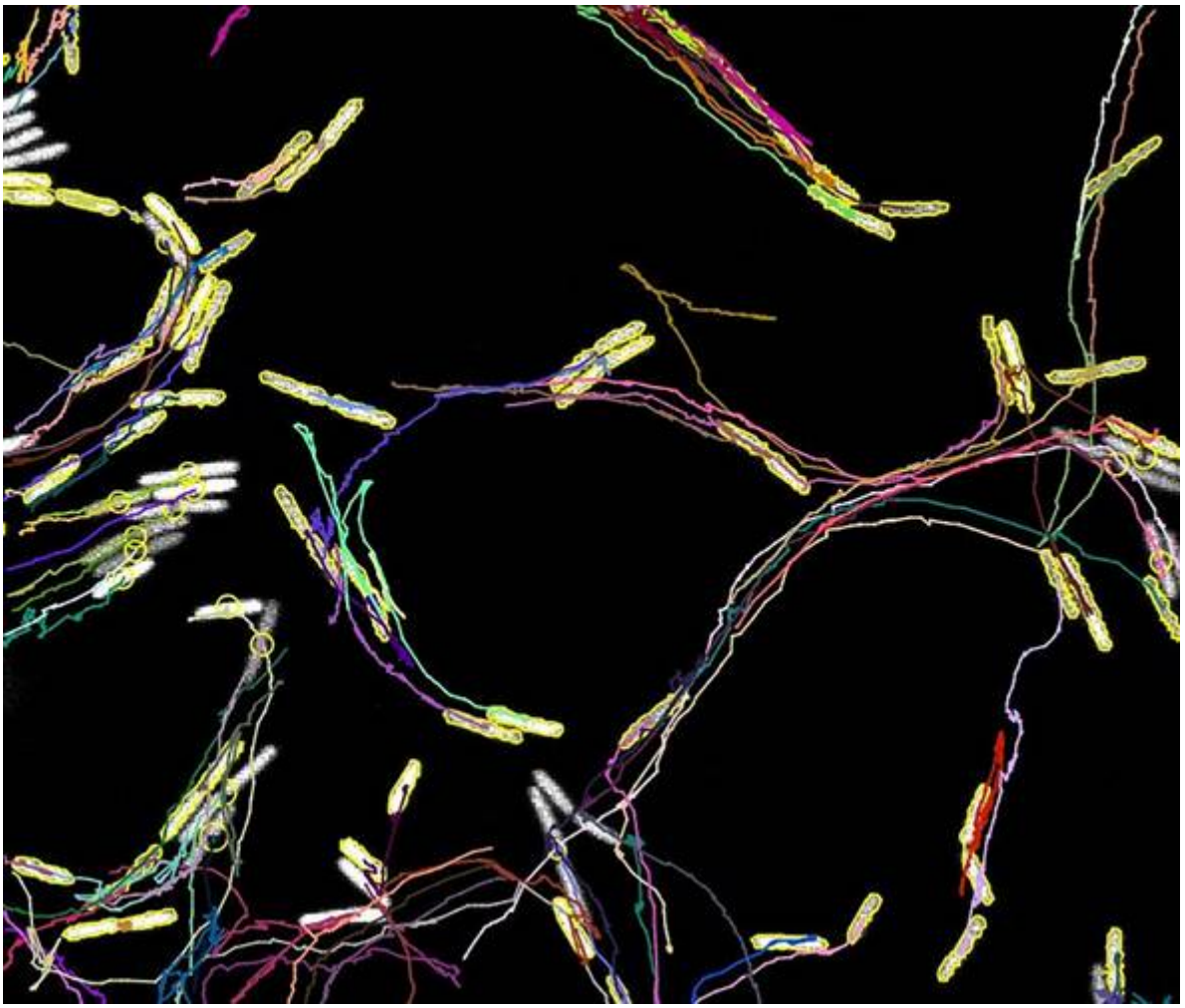

Foto: Se hace camino al andar. Celeste Dea. 1er puesto. Concurso fotográfico SAMIGE 20 años.

13 - Microbiología Molecular y Fisiología

HOST-SPECIFIC EVOLUTION OF NDM CARBAPENEMASES

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The indiscriminate use of antibiotics is accelerating the rise of resistant microorganisms, to last resort drugs such as carbapenems. Metallo-?-lactamases (MBLs), the largest group of carbapenemases, can inactivate these antibiotics and are of main concern due to their rapid dissemination and the absence of clinical inhibitors. The most clinically relevant MBLs are NDMs, VIMs, IMPs and SPM-1, with NDMs being the most widespread, characterized by their lipidation and anchoring to the outer membrane of Gram-negative bacteria. These enzymes fold and acquire their cofactor Zn(II) in the periplasmic space, where metal levels are not regulated but instead depend on extracellular availability. During infection, neutrophils from the human immune system sequester metal ions at the host-pathogen interface depriving bacteria of essential nutrients. In previous studies in *E. coli*, we demonstrated that this Zn(II) deprivation impacts on the activity and stability of MBLs in the periplasm. In the case of NDM-1, leads to its degradation by the periplasmic protease Prc. This reduced stability explains the clinical evolution of NDMs into variants more resistant to periplasmic degradation. However, remains unclear how protein quality control mechanisms affect NDM-1 in other clinical strains. MBLs were expressed in *E. coli* ATCC 25922, *A. baumannii* ATCC 17978 and *P. aeruginosa* PAO1. The metal restriction was induced by the addition of dipicolinic acid (DPA), and protein levels were determined by immunodetection. *E. coli* and *A. baumannii* expressing either NDM-1 or a typical serine-?-lactamase were exposed to human neutrophils and/or imipenem in DMEM medium, bacterial survival was assessed by measuring CFUs relative to untreated controls. Minimal inhibitory concentrations were measured according to CSLI guidelines, and knock-outs of *A. baumannii* crafted by CRISPR-Cas or suicide vector techniques. NDM-1 was 7 times more susceptible to Zn(II) limiting conditions in *A.* baumannii than in the other hosts. We identified CtpA as the major protease involved in the degradation of NDM-1 in *A. b*aumannii. This protease is distantly related to *E. coli* Prc, and the difference in the proteolysis mechanism would explain the variation in NDM-1 stability between both hosts. Notably, several clinical NDM variants show highly stability improvement over NDM-1 in *A. baumannii* than in *E. coli*, indicating a host-specific effect on variant selection. Furthermore, *A. baumannii* expressing NDM-1 was more sensitive to the presence of neutrophils and antibiotics compared to *E. coli*. Taken together, these results suggest that the evolution of NDMs could be driven not only by tolerance to zinc-limiting conditions but also by adaptability to the different

periplasmic environments where this enzyme may be found. Based on these insights, host-specific therapies could be designed targeting NDMs.

Palabras clave: AcineAcinetobacter baumannii-NDM-Zinc-Proteolysis-Bacterial Resistance