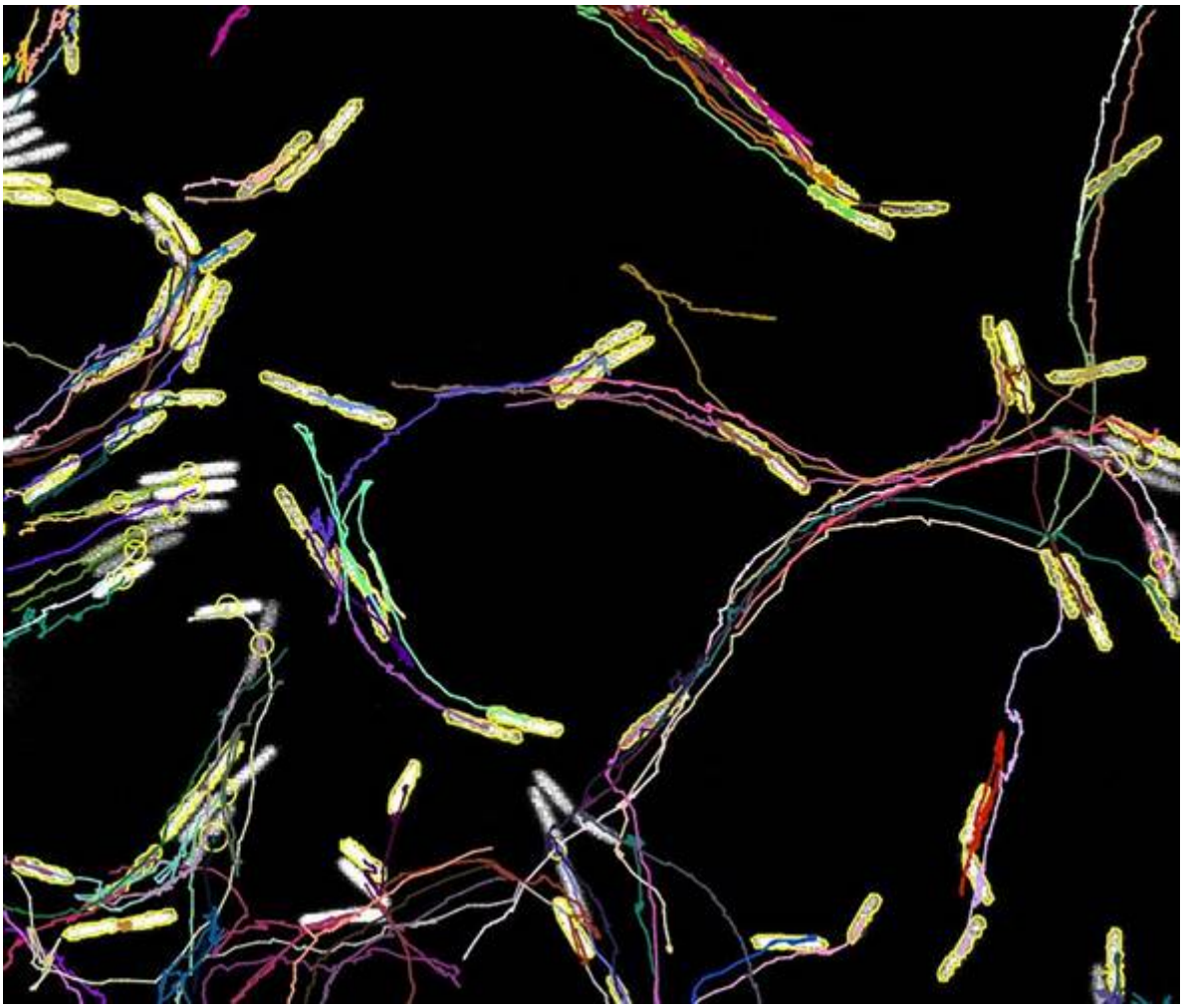
Sociedad Argentina de Microbiología General

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.



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CROSS-PROTECTION MEDIATED BY ?-LACTAMASE-PRODUCING *Klebsiella pneumoniae* ON CARBAPENEM RESISTANCE IN COEXISTING BACTERIA

Feser Ernestina[1,2*] - Gonzalez Soto Ana María[3,4*] - Munita José Manuel[3,4] - Vila Alejandro José[1,2] - López Carolina[1]

1) Instituto de Biología Molecular y Celular de Rosario (IBR-CONICET), Rosario, Santa Fe, Argentina
2) Universidad Nacional de Rosario (UNR), Rosario, Santa Fe, Argentina
3) Genomics & Resistant Microbes group (GeRM), Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile
4) Multidisciplinary Iniciative for Collaborative Research on Bacterial Resistance (MICROB-R), Santiago, Chile
Contacto: feserernestina@gmail.com

Antibiotic resistance to ?-lactams, particularly carbapenems, poses a significant challenge in treating bacterial infections. One major resistance mechanism is the production of ?-lactamases (BLs), hydrolytic enzymes that degrade ?-lactams. Bacterial responses to antibiotics are heavily influenced by interactions with other microorganisms. However, these interactions are often overlooked in determinations of pathogen sensitivity to antibiotics. Specifically, BL production by one bacterium can reduce the availability of active drug, acting as a "shared resource" that benefits other coexisting bacterial species. Outer membrane vesicles (OMVs) play a crucial role in mediating cooperative interactions among co-infecting bacteria by transporting BLs and the genes encoding them. This transport enhances the survival of the bacterial community. This work focused on studying the role of OMVs in these dynamics by using carbapenemase-producing *Klebsiella pneumoniae* (Kp) strains—ranked as the top bacterial pathogens by the WHO for 2024—and *Pseudomonas aeruginosa* (Pa). Both Pa and Kp are commonly found in mixed communities and are prevalent in polymicrobial infections associated with urinary tract infections and chronic wounds. We evaluated the effect of co-cultures on antibiotic resistance by minimum inhibitory concentration (MIC) determinations of mono- and co-cultures against imipenem (IMP) and subsequently distinguished Kp from Pa by plating onto a differential chromogenic culture medium. This revealed the ability of Kp expressing *bla*NDM-1 or *bla*NDM-7 (NDM: New Delhi Metallo- ?-lactamase) to cross-protect Pa against IMP, with a greater shielding effect observed in the case of NDM-7. In contrast, Kp expressing blaKPC-2 (KPC: *Klebsiella pneumoniae* carbapenemase) or carrying the empty vector (EV) did not protect IMP-susceptible Pa. Given that effective protection occurred with Kp expressing NDM-1 or NDM-7—lipoproteins anchored to the outer membrane—and was negligible with KPC-2, a soluble periplasmic ?-lactamase, we investigated the

role of OMVs from Kp in packaging these BLs and their contribution to cross-protection. OMVs were purified from solid medium of Kp carrying EV or expressing BLs, and from clinical isolates producing NDM-5 or NDM-7. OMVs from Kp were enriched with NDM-type enzymes compared to KPC-2 and exhibited greater activity against nitrocefin. Co-incubation of OMVs from Kp *bla* NDMs with imipenem-susceptible Kp or Pa cells improved their survival up to 128 µg/mL of IMP, whereas OMVs from Kp *bla*KPC-2 only allowed growth up to 1 µg/mL. The findings with the laboratory strain were also applicable to OMVs purified from clinical isolates, showing high levels of NDMs in their active form into vesicles. Our results indicate that carbapenemase-producing Kp strains, particularly those with NDMs, highly prevalent in clinical isolates in Argentina and Chile, can protect other coexisting bacteria. Future research will investigate whether the enzyme-mediated protection is coupled with genetic material transfer.

Palabras clave: carbapenem resistance - polymicrobial infections - Klebsiella pneumoniae - Pseudomonas aeruginosa - outer membrane vesicles