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IS*CR* Elements Are Key Players in IncA/C Plasmid Evolution

In the recent paper by Call et al. (1), the authors show that sequence analysis of their IncA/C plasmids revealed that antimicrobial resistance genes were grouped in four main regions in addition to the region that harbors the bla_{CMY} gene in an otherwise highly related plasmid backbone structure. The authors show that the *floR* resistance region is found in all three plasmids as well as in the pSN254 plasmid and is found in close proximity to what the authors (and also a previous paper [9]) call *insA*. The authors also note that another antibiotic resistance gene cluster includes the resistance gene *aadA* which is found in three of these plasmids and is always found adjacent to an insertion sequence termed *insE* (9). These two insertions, *insE* and *insA*, are typical of insertion sequences previously designated IS*CR* elements (6, 7). IS*CR* elements are closely related to an unusual family of insertion sequences called the IS*91* family (6, 7). These elements are known to move by a process called rolling-circle replication, and a function of this process is the concomitant movement of additional sequences found upstream of their transposase genes (5). To be specific, *insE* is indeed IS*CR2*, and *insF* is IS*CR16* (8). IS*CR* elements are now recognized as powerful antibiotic resistance gene capture and movement systems that are also capable of constructing extended clusters of antibiotic resistance genes on plasmids as well as on chromosomes (7). The IncA/C plasmid group is now known to be very widely distributed both geographically and in many species of bacteria because of the plasmids' promiscuous behavior (3, 4). The IncA/C reference plasmid, pRA1, isolated in 1971 from the fish pathogen *Aeromonas hydrophila* harbors IS*CR2* (2), indicating that this element has been closely involved in recruiting antibiotic resistance genes with IncA/C plasmids for some time. IS*CR2* is often found in close proximity to the *sul2* gene and a truncated *glmM* gene as a conserved resistance array among IncA/C plasmids; IS*CR2* is often called an IS*Vsa*3-like IS element or simply *orfA* (2). Interestingly, a recent publication has indicated that the ICE element SXT shares a common ancestor with the IncA/C plasmids (2), and IS*CR2* together with truncated copies of this element are always found as part as SXT, implicating IS*CR2* in the construction of this element (6). The IS*CR16* element appears to be a more recent addition to the IncA/C plasmids and has been found in only three plasmids so far and always adjacent to *groEL* or *groES* gene(s) (8). This also is very interesting as this element and the closely related elements IS*CR3* and IS*CR4* are also found adjacent to sections of *groEL* as well as resistance genes, which has allowed us to track the evolutionary history of this element (8). Therefore, it appears that IS*CR* elements are key players in the recent evolution of the IncA/C plasmid group. Furthermore, gene capture systems such as IS*CR* elements allied with the promiscuous nature of IncA/C plasmids provides a new and powerful combination for rapid dissemination of antibiotic resistance genes.

REFERENCES

1. **Call, D. R., R. S. Singer, D. Meng, S. L. Broschat, L. H. Orfe, J. M. Anderson, D. R. Herndon, L. S. Kappmeyer, J. B. Daniels, and T. E. Besser.** 2010. bla_{CMY-2}-positive IncA/C plasmids from *Escherichia coli* and *Salmonella enterica* are a distinct component of a larger lineage of plasmids. Antimicrob. Agents Chemother. **54:**590–596.
2. **Fricke, W. F., T. J. Welch, P. F. McDermott, M. K. Mammel, J. E. LeClerc, D. G. White, T. A. Cebula, and J. Ravel.** 2009. Comparative genomics of the IncA/C multidrug resistance plasmid family. J. Bacteriol. **191:**4750–4757.
3. **Kim, M. J., I. Hirono, K. Kurokawa, T. Maki, J. Hawke, H. Kondo, M. D. Santos, and T. Aoki.** 2008. Complete DNA sequence and analysis of the transferable multiple-drug resistance plasmids (R plasmids) from *Photobacterium damselae* subsp. *piscicida* isolates collected in Japan and the United States. Antimicrob. Agents Chemother. **52:**606–611.
4. **Pan, J. C., R. Ye, H. Q. Wang, H. Q. Xiang, W. Zhang, X. F. Yu, D. M. Meng, and Z. S. He.** 2008. *Vibrio cholerae* O139 multiple-drug resistance mediated by *Yersinia pestis* pIP1202-like conjugative plasmids. Antimicrob. Agents Chemother. **52:**3829–3836.
5. **Tavakoli, N., A. Comanducci, H. M. Dodd, M. C. Lett, B. Albiger, and P. Bennett.** 2000. IS*1294*, a DNA element that transposes by RC transposition. Plasmid **44:**66–84.
6. **Toleman, M. A., P. M. Bennett, and T. R. Walsh.** 2006. Common regions e.g. orf513 and antibiotic resistance: IS*91*-like elements evolving complex class 1 integrons. J. Antimicrob. Chemother. **58:**1–6.
7. **Toleman, M. A., P. M. Bennett, and T. R. Walsh.** 2006. IS*CR* elements: novel gene-capturing systems of the 21st century? Microbiol. Mol. Biol. Rev. **70:**296–316.
8. **Toleman, M. A., and T. R. Walsh.** 2008. Evolution of the IS*CR3* group of IS*CR* elements. Antimicrob. Agents Chemother. **52:**3789–3791.
9. **Welch, T. J., W. F. Fricke, P. F. McDermott, D. G. White, M. L. Rosso, D. A. Rasko, M. K. Mammel, M. Eppinger, M. J. Rosovitz, D. Wagner, L. Rahalison, J. E. Leclerc, J. M. Hinshaw, L. E. Lindler, T. A. Cebula, E. Carniel, and J. Ravel.** 2007. Multiple antimicrobial resistance in plague: an emerging public health risk. PLoS One **2:**e309.

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Author's Reply

This is an appropriate clarification of nomenclature and is a useful contribution.

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