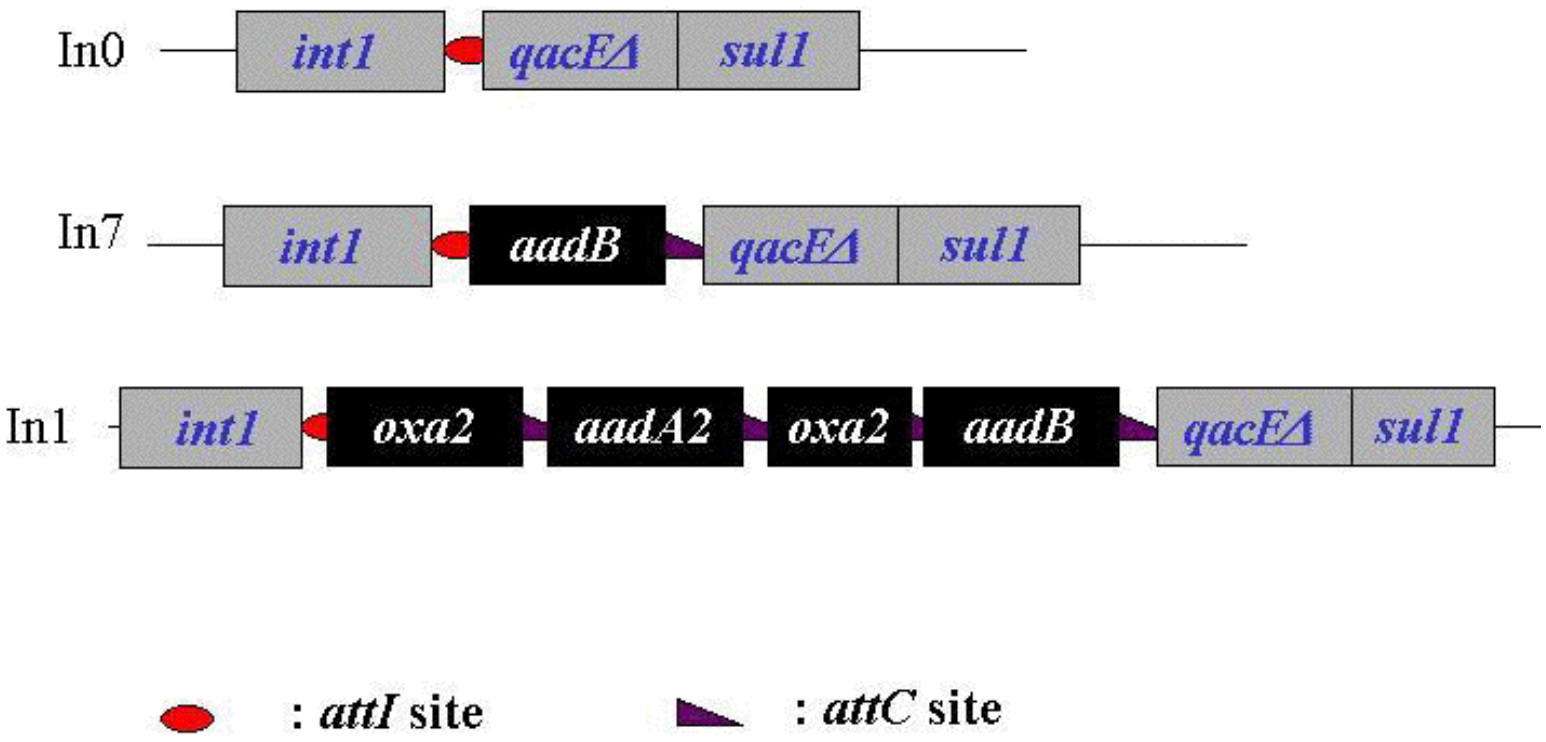
Integrons

In recent years, the threat caused by the acquisition of antibiotic resistance by pathogenic bacteria has been growing. The number of deaths caused by nosocomial infections are increasing and strains of four potentially deadly pathogens (Enterococcus faecalis, Mycobacterium tuberculosis, Pseudomonas aeruginosa, and Staphylococcus aureus) have been found which are resistant to all previously known antibiotics. Bacteria can become resistant either through mutation or via horizontal transfer by transformation, transduction, or conjugation. Perhaps the most common of these methods of transferring antibiotic resistance is conjugation. In this manner, plasmids and transposons carrying antibiotic resistance genes can readily move from one cell to another. Recently, another class of mobile DNA elements have been discovered that can transfer antibiotic resistance.

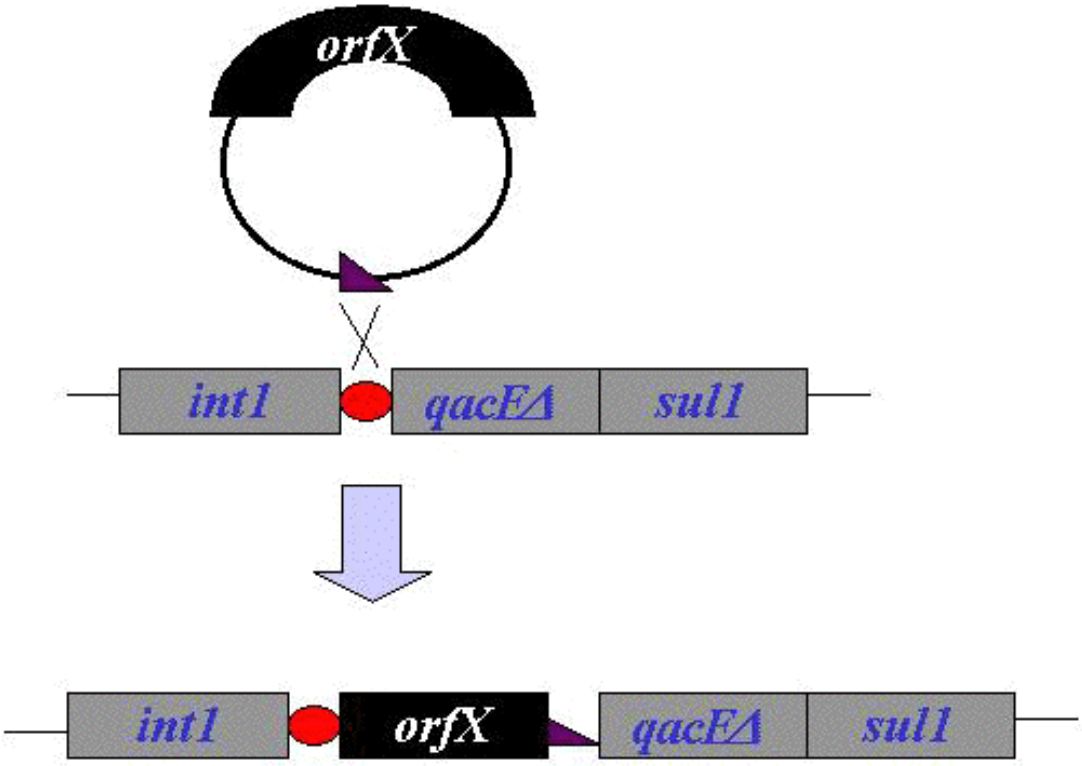
In 1986, the DNA sequence of several seemingly unrelated antibiotic resistance genes heralded the first hints regarding integrons. Common regions were noted upstream and downstream of various antibiotic resistance genes. These regions were found to be in different places on various plasmids, suggesting that, like transposons, these elements were mobile. However, the element differed from transposons in two important characteristics: (i) Transposons have direct or indirect repeat sequences at their ends, but the regions surrounding the antibiotic resistance genes in the new elements were not repeats, and (ii) the elements contained a site-specific integrase gene of the same family as those found in phage but lacked many gene products associated with transpositon. Due to these differences, the elements were not grouped with transposons and were named integrons.

Integrons are mobile DNA elements with the ability to capture genes, notably those encoding antibiotic resistance, by site-specific recombination. Integrons have an intergase gene (int), a nearby recombination site (attI), and a promoter, Pant. There are at least three classes of integrons based upon the type of integrase gene they possess. Class 1 integrons have been examined the most extensively. They consist of a variable region bordered by 5' and 3' conservered regions. The 5' region is made up of the int gene, attI, and the promoter Pant which drives transciption of genes within the variable region. The 3' region consists of an ethidium bromide resistance locus (qacED1), a sulfonamide resistance gene (sulI), and an open reading frame containing a gene of unknown function. The integrase of Class 2 integrons is located within the 3' conserved region. Class 3 integrons have yet to be thoroughly studied. The organization of class 1 integrons is shown below.

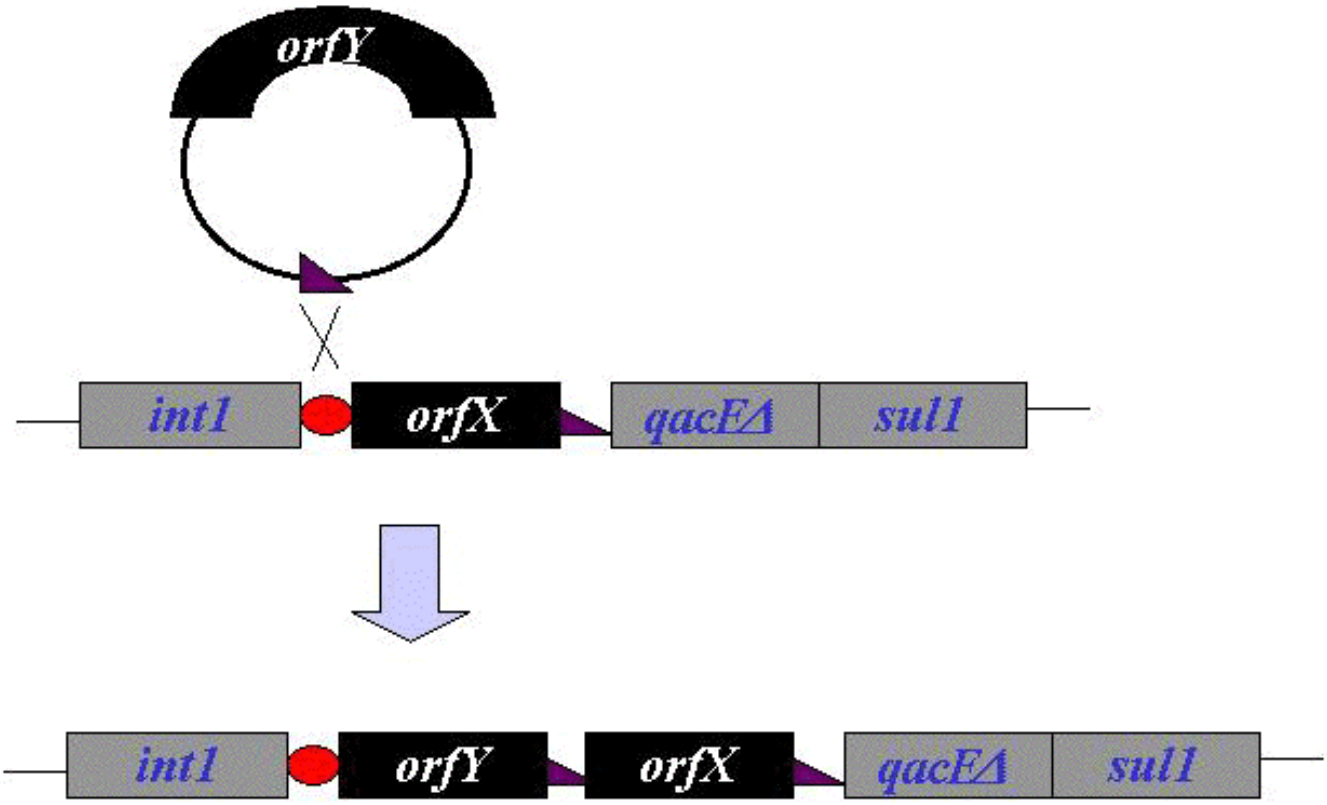


The antibiotic resistance genes that integrons capture are located on gene cassettes. The cassettes consist of a promoterless

gene and a recombination site (attC). The cassettes can exist as free, circular DNA but cannot be replicated or transcribed in this form. A recombination event occurs between attI and attC, integrating the cassette into the integron. The gene on the cassette is then bound by the attI site on the 5' side and by attC on the 3' side.



Additional gene cassettes can integrate at attI or attC, resulting in the integration of several genes into the variable region. The promoter, Pant, allows expression of these genes, with the gene closest to the promoter having the highest level of expression. The cassettes can by "shuffled" (via excision and reintegration) so the cassette containing the gene that encodes resistance to the antibiotic in the environment will be closest to the promoter. In this manner, the resistance gene necessary for the survival will be maximally expressed.



Current research on integrons is focused on two areas: (i) identifying new integrons and cassettes from clinical isolates, and (ii) determining the molecular mechanism of integration of cassettes into the integron. Identification of integrons is straightforward because the int gene and the integrations sites make convenient targets for the creation of primers for PCR. The amplified DNA can then be sequenced and any genes within it can be identified. Mutational studies have identified regions in both the integrase and the integration sites that are important for binding and recombination.

Many questions regarding integrons still need to be answered. What was the origin of integrons and the gene cassettes? (Bacterial isolates from 1888 have been found to contain gene cassettes, so they predate the use of antibiotics by humans.) Can genes other than antibiotic resistance genes be mobilized by integrons? How do integrons integrate into host DNA?

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Written by Mark Waites while a student in Microbiology at the University of Illinois, Urbana- Champaign
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Please send comments, suggestions, or questions to smaloy@sciences.sdsu.edu