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Studies on DNA gyrases of *Campylobacter jejuni* as the target of quinolones
(キノロン剤の標的としての*Campylobacter jejuni* DNAジャイレースの性状)

Campylobacter jejuni is considered one of the most important human pathogenic bacteria. Quinolones belong to a family of broad-spectrum synthetic antimicrobials, particularly ciprofloxacin, have been used for the treatment of *Campylobacter* infections in patients with invasive disease. However, excessive use of quinolones in veterinary medicine caused increase emergence of quinolone-resistant *C. jejuni*. Recently, quinolone resistance in *C. jejuni* from food animals is now recognized as an emerging public health problem. For appropriate treatment, the assessment of antimicrobial susceptibility is essential. However, *C. jejuni*, the microaerophilic fastidious bacteria, present problems in antimicrobial susceptibility testing related to particular cultural requirements and their slow growth. Hence, development of an *in vitro* method for studying the activity of quinolones against the DNA gyrase of *C. jejuni* seemed to be necessary.

In this regard, in Chapter I, I have succeeded in producing and purifying *C. jejuni* DNA gyrase, which is the sole target of quinolones. SIT showed the highest inhibitory activity, and the analysis of the quinolone structure-activity relationship demonstrated that a fluorine atom at R-6 might play the important role in the inhibitory activity against *C. jejuni* gyrase. Moreover, the results of this chapter suggested that the *in vitro* supercoiling

inhibition assay may be a useful and predictive technique to monitor the antibacterial potency of quinolones.

In Chapter II, I elucidated the contribution of amino acid substitutions in GyrA of *C. jejuni* DNA gyrase; Thr86Ile, Thr86Ala, Thr86Lys, Asp90Asn, and Asp90Tyr to quinolone resistance. The quinolone-inhibited supercoiling assay demonstrated the important role of these amino acid substitutions, especially Thr86Ile, in reduced sensitivity to quinolone. SIT showed the highest inhibitory activity against mutant *C. jejuni* gyrase

SIT was shown to be the most effective inhibitor of WT and mutant DNA gyrases, amongst the five quinolones studied here. Hence, my results demonstrated that SIT might be a candidate for the treatment of campylobacteriosis caused by CIP-resistant *C. jejuni*.