The Mannose Transporter Complex: an Open Door for the Macromolecular Invasion of Bacteria

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In this issue of the Journal of Bacteriology, Bieler et al. demonstrate (i) that the toxic activity of microcin E492 is independent of the “route of administration,” viz. whether it is added from the outside (as in nature) or expressed endogenously in the cytoplasm, and (ii) that microcin E492 requires the transporter for mannose to deploy its ion channel-forming activity. This is the strongest and most direct evidence to date that the mannose transporter is involved in microcin activity in gram-negative enterobacteria.

Bacteriocins, colicins, and microcins are proteins produced by gram-positive and gram-negative bacteria to ward off closely related competitors (5). Compared with the other means of bacterial defense, viz. secondary metabolites with antibiotic properties, hydrolytic enzymes, and exotoxins, the microcins have high specificity and potency. “Communication” through bacteriocins may establish a balance of power between bacterial communities and thus maintain the astounding diversity of microbes in nature (2, 14). Bacteriocins are a heterogeneous family of proteins that vary in size from heptapeptides containing modified amino acids (lantibiotics) to proteins of up to 40 kDa. They inhibit the growth of bacteria by forming ion channels in the cytoplasmic membrane, degrading DNA, blocking protein synthesis, or inhibiting peptidoglycan synthesis (24).

Class IIa bacteriocins and bacteriophage lambda DNA also rely on these molecules in or across the inner membrane: class IIa bacteriocins are produced by gram-positive bacteria (5). They are unrelated to microcin E492 as far as size and sequence are concerned. Resistance of Listeria spp. to IIa bacteriocins was correlated with the following phenotypes: (i) absence of IAB\textsubscript{Man} in the proteomes of resistant bacteria (however, only the soluble IAB and not the membrane-inserted IIC and IID can be detected on standard two-dimensional gels) (22), (ii) mutations in the $\sigma^{54}$ (rpoN) factor and the $\sigma^{54}$-dependent transcription activator ManR of the Listeria mpt operon (homologous to the Escherichia coli man operon) (3, 10, 29), (iii) a (polar?) mutation in the promoter proximal mptA (IIA) cistron (22), and (iv) in-frame deletions in the mptD (IID) gene (which may have compromised the folding of mannose transporters). In some mutants, the presence of the IIC Man and/or IID Man subunit was not sufficient to rescue resistance to microcin E492, and the IIC Man (ManY) and IID Man (ManZ) subunits are required for microcin activity.

Bieler et al. demonstrate that at least 11 C-terminal residues of microcin E492 (15) which are essential for penetration across the outer membrane probably are not essential for penetration into the inner membrane, and definitely are not essential for activity from inside. On the other hand, all modifications that favor membrane insertion from the inside increase the toxic efficacy of the cytoplasmically expressed microcin E492, viz. a cis-active N-terminal leader/targeting sequence or a trans-active mutant secretion system that can secrete proteins without a signal sequence. Bieler et al. further present convincing evidence that microcin E492 can insert directly from the cytoplasm into the inner membrane without the detour of export and reinsertion from the periplasmic face.

The susceptibility of the target cells to bacteriocins is contingent first on receptors in the outer membrane and second on a number of outer membrane, periplasmic, and inner membrane proteins, such as the Ton and Tol pathways (4, 16, 27). These proteins, which normally mediate the uptake of iron chelates and vitamins, are utilized as carriers for the translocation of the bacteriocin to its molecular target. However, there are some inner membrane proteins that not only are “parasitized” transiently as carriers but also act as “cofactors” of bacteriocin action.
These results suggest that the interaction between IIC and IID may be important for stability but that it is most probably IIC that determines the high specificity for microcin E492 and class IIa bacteriocins.

The molecular determinants of IIC and/or IID for interaction with microcin E492 could be identified with mutations that confer microcin resistance but continue to allow the transportation and phosphorylation of mannose. Such mutants could be selected with mannose as the only carbon source and with microcin E492 as the counterselectant.

FIG. 1. Topology model of the mannose transporter complex. His-10 and His-175 of IAB<sup>amin</sup> (ManX) transfer phosphate from phospho-HPr (PstH) to the sugar that is translocated by the IIC/IID (ManY/ManZ) complex. The highly specific interaction between microcin E492 and the membrane-spanning IIC and/or IID subunits causes inner membrane depolarization. HPr is phosphorylated with phospho-epimerase (PEP) by enzyme I (PstI) of the phosphotransferase system. The model is predicted according to reference 18 with the constraints from references 11 and 13.

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