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Innexins: a family of invertebrate gap-junction proteins

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In vertebrates, intercellular communication via gap junctions is mediated by the connexin family of molecules, which is made up of at least 13 members (reviewed in Ref. 1). These proteins, which have four transmembrane domains and intracellular C- and N-termini, oligomerize to form hemichannels. Oligomers in the adjacent membranes of two closely apposed cells ‘dock’ to form intercellular channels, through which ions and small molecules move.

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Intercellular communication is a fundamental function of any multicellular organism and it is odd that no obvious homologues of the connexins have been found in any invertebrate. In view of the fact that over 90% of the genomic sequence of *Caenorhabditis elegans* is available for analysis, it is becoming increasingly unlikely that invertebrate connexins will be found.

Conventional genetic dissection of *C. elegans* and *Drosophila*, however, has identified a gene family with some role in gap-junction communication. Although they bear no sequence similarity to the connexins, these genes are predicted to encode proteins with the same topology. In *C. elegans*, mutations in the *unc-7* gene result in an uncoordinated phenotype, and the formation of ectopic electrical junctions between some interneurons and motoneurons (J.G. White, E. Southgate and J.N. Thomson, cited in Ref. 2). A worm with an eating disorder results from mutations in the *eat-5* gene; here, some pharyngeal muscles fail to establish normal electrical connections with their neighbours². In *Drosophila*, one of the transcripts from the *shaking-B* locus [*shaking-B(neural)*; also known as *Passover*] is required for electrical synapse function between neurons of the giant-fibre escape circuit^{3,4} and between embryonic somatic muscles (J.P. Bacon *et al.*, 1996, *Soc. Neurosci. Abstr.* 22, 38). A second transcript from this *Drosophila* locus, known as *shaking-B(lethal)*, the *Drosophila* gene *optic ganglion reduced* (*ogre*), and several other *C. elegans* genes share sequence similarity with this family⁵ but their mutant phenotypes have not yet been fully characterized. These worm and fly data did provide some circumstantial evidence that these loci encode gap-junction proteins. They were given the name OPUS (for *ogre*, *passover*, *uncoordinated*, *shaking-B*) in a previous letter to *TIG* (Ref. 6).

We feel that the name OPUS is confusing because we now know that *Passover* and *shaking-B* are allelic and it has recently been brought to our attention that *opus* is the name of a *Drosophila copia*-like transposable element⁷. In addition, the recent determination of the role of one of these genes makes it timely to rename this family in a way that reflects function. Using heterologous expression in *Xenopus* oocyte pairs, it has been demonstrated unequivocally that *Shaking-B(lethal)* protein is sufficient to form homotypic gap junctions⁸. Interestingly, the closely related *Shaking-B(neural)* protein fails to form functional junctions in this system. We suspect that either *Shaking-B(neural)* forms gap junctions that are closed under the particular physiological conditions of *Xenopus* oocytes, or that it requires a partner to form hetero-oligomeric channels; a few connexins fail to form homotypic junctions in *Xenopus* oocytes (reviewed in Ref. 1).

Despite these remaining uncertainties about the function of *Shaking-B(neural)* protein, *Shaking-B (lethal)* is the first invertebrate gap-junction protein to be identified. It means that this family of genes, and their proteins, can be given a functional name. We propose the name *innexins* (invertebrate analogues of the connexins) for invertebrate gap-junction proteins. We are anxious to avoid the gratuitous proliferation of names in an already overstuffed literature but we think it better to choose a name that reflects function rather than an acronym based on an incomplete set of mutant phenotypes.

It will be important to examine the function of fly and worm *Shaking-B(lethal)*-like proteins, using heterologous expression systems, to determine whether they truly are *innexins*.

Judging from the vertebrate connexin data, we anticipate that the innexin family will have many members that can either work alone or in concert to build a range of gap-junction types. Another task is to look for innexins in other invertebrate phyla; so far they have been described only in insects and nematodes. Given the recent proposal that moulting animals form a new phyletic clade, the Ecdysozoa⁹, it remains a real possibility that innexin proteins are a molecular marker for this clade, and will not be found outside it.

Interestingly, our standard BLAST searches of the protein databases at the NCBI server have revealed no vertebrate proteins with sequence similarity to Shaking-B. Whether the similar (predicted) topology, without obvious sequence similarity, of innexins and connexins is a case of convergent evolution or one of extreme sequence divergence within a protein family, remains to be determined.

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FIGURE 1.

The topology of invertebrate innexins, with four transmembrane domains and intracellular C- and N-termini, is the same as the vertebrate connexins (a). After injection of *shaking-B(lethal)* mRNA into a pair of *Xenopus* oocytes and their subsequent manipulation into contact (b), incremental step depolarizations of the left oocyte elicit junctional currents, under voltage clamp, in the right oocyte (c). We conclude that Shaking-B(lethal) protein is a structural component of invertebrate gap junctions. [Data in (c) are similar to those in Ref. 8.]