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The function and evolution of *Wnt* genes in arthropods

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ABSTRACT

Wnt signalling is required for a wide range of developmental processes, from cleavage to patterning and cell migration. There are 13 subfamilies of *Wnt* ligand genes and this diverse repertoire appeared very early in metazoan evolution.

In this review, we first summarise the known *Wnt* gene repertoire in various arthropods. Insects appear to have lost several *Wnt* subfamilies, either generally, such as *Wnt3*, or in lineage specific patterns, for example, the loss of *Wnt7* in *Anopheles*. In *Drosophila* and *Acyrthosiphon*, only seven and six *Wnt* subfamilies are represented, respectively; however, the finding of nine *Wnt* genes in *Tribolium* suggests that arthropods had a larger repertoire ancestrally.

We then discuss what is currently known about the expression and developmental function of Wnt ligands in *Drosophila* and other insects in comparison to other arthropods, such as the spiders *Achaearanea* and *Cupiennius*. We conclude that studies of *Wnt* genes have given us much insight into the developmental roles of some of these ligands. However, given the frequent loss of *Wnt* genes in insects and the derived development of *Drosophila*, further studies of these important genes are required in a broader range of arthropods to fully understand their developmental function and evolution.

1. Introduction

Wnt signalling regulates many developmental processes, including the maintenance of stem cells, cell division, migration, patterning and death (Logan and Nusse, 2004), and therefore is a major part of the developmental 'toolkit' of animals (Carroll et al., 2004).

Wnt genes encode secreted glyco-protein ligands that bind to transmembrane receptors expressed by target cells, thereby triggering a cascade of interactions among a complex array of intracellular proteins to activate or repress gene expression. In the so-called 'canonical' Wnt pathway, Wnt ligands bind to transmembrane receptors encoded by *frizzled* genes. This results in the release of Armadillo/β-catenin from a protein complex that otherwise promotes its degradation. The degradation complex includes proteins such as Axin and APC. The released β-catenin can then bind to the transcription factor Pangolin/TCF and enter the nucleus to regulate gene expression (van Amerongen and Nusse, 2009). However, this is rather an over-simplification of the complexity of Wnt signalling. Not only are there multiple *frizzled* genes (four in *Drosophila*), but Wnt ligands can also bind to other receptors such as the Ror and Derailed/Ryk receptor tyrosine kinases. Wnt signalling can also operate independently of β-catenin and TCF in what are called 'non-canonical' pathways (Croce and McClay, 2008; van Amerongen and Nusse, 2009).

The complexity of Wnt signalling is not only found at the level of the receptors and intracellular machinery, however, as 13 distinct subfamilies of *Wnt* ligand genes are found in metazoans. This diversity in the repertoire of *Wnt* genes appeared very early in the evolution of animals because 12 *Wnt* subfamilies are represented in the cnidarians *Nematostella vectensis* and *Hydra magnipapillata* (Kusserow et al., 2005; Lee et al., 2006; Lengfeld et al., 2009) (Fig. 1). *Wnt* gene diversity has been maintained in many deuterostomes and has increased in lineages where there have been genome duplications such as vertebrates (Fig. 1). Recently it has been shown that lophotrochozoans, a sister clade of ecdysozoans, also possess a diverse repertoire of *Wnt* genes (Cho et al., 2010).

With respect to arthropods, *Drosophila* contains seven *Wnt* genes (Fig. 1), and it is in the fruit fly that the function of the *Wnt* genes has been most comprehensively investigated. In other arthropods, particularly crustaceans, myriapods and chelicerates, comparatively little is known about the expression and function of *Wnt* genes. Indeed, even for some *Drosophila Wnt* genes, for example, *Wnt6* and *Wnt10*, only the expression has been described (Janson et al., 2001). In this review we first discuss the evolution of the *Wnt* gene repertoire among arthropods. We then review the function of the Wnt ligands during *Drosophila* development and

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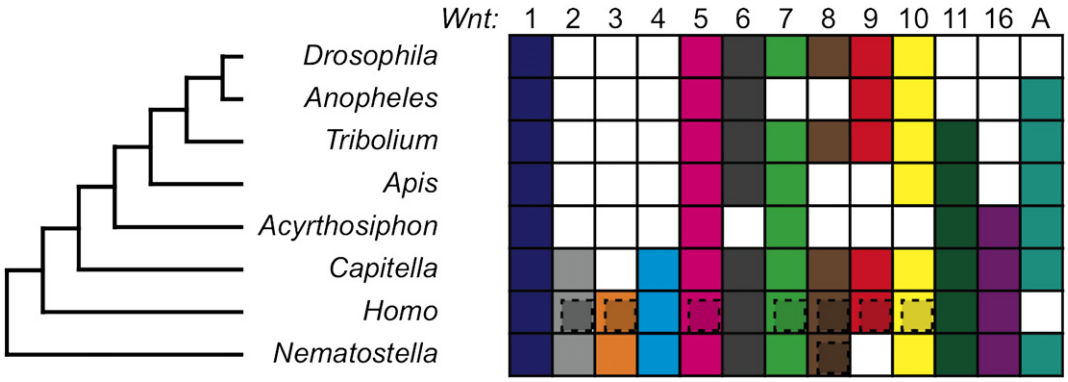

Fig. 1. The *Wnt* gene repertoire of arthropods and other metazoans. The *Wnt* subfamilies (1–11, 16 and A) found in various arthropods and other metazoans are represented by coloured boxes. White boxes indicate the loss of particular *Wnt* subfamilies. Duplicated *Wnt* genes are represented by inset boxes with dotted lines. Note that *Wnt8* is also called *WntD* in *Drosophila* and *Tribolium*. The phylogenetic relationships of the various animals are indicated by the tree on the left (Bolognesi et al., 2008a; Cho et al., 2010; Dearden et al., 2006; Kusserow et al., 2005; Lee et al., 2006; Shigenobu et al., 2010).

what has been garnered from the few studies to date that have investigated the expression and function of these genes in other arthropods. We suggest that further studies of *Wnt* genes and other Wnt signalling components in a broader range of arthropods will be insightful for a number of reasons. Not only will such studies allow better understanding of Wnt signalling mechanisms per se, they will also allow further dissection of the genetics underlying many important developmental processes, from the maintenance of stem cells to segmentation and cell migration. Furthermore, systematic analysis of *Wnt* genes in various different arthropods will provide better understanding of developmental evolution in these animals and in metazoans in general.

2. The *Wnt* gene repertoire of arthropods

Comparison of the *Wnt* gene repertoire between insects with sequenced genomes and other metazoans reveals striking patterns of *Wnt* gene loss in particular insect lineages and among these animals in general (Fig. 1) (Bolognesi et al., 2008a; Dearden et al., 2006; Kusserow et al., 2005; Lee et al., 2006; Lengfeld et al., 2009; Shigenobu et al., 2010). While *Drosophila* has seven *Wnt* genes, in the mosquito *Anopheles gambiae* and the pea aphid *Acyrthosiphon pisum* only six subfamilies are represented (Bolognesi et al., 2008a; Shigenobu et al., 2010). Orthologues of *Wnt2* and *Wnt4* appear to have been lost in all insects and a *Wnt16* gene has only been reported in the pea aphid (Shigenobu et al., 2010). Furthermore, *Wnt11* has probably been lost in dipterans and there is no *WntA* in *Drosophila* (Fig. 1). However, it is not clear if these patterns of loss are a reflection of arthropods in general. Therefore, it would be very interesting to determine the *Wnt* repertoire of crustaceans, chelicerates and myriapods in comparison to insects as a basis for functional comparison of these important developmental genes.

2.1. *Wnt* gene clusters

Analysis of the genomic organisation of *Wnt* genes in metazoans has shown that some of these genes are found in two clusters that are presumably ancestral (Bolognesi et al., 2008a; Cho et al., 2010; Sullivan et al., 2007). The *Wnt9–wingless–Wnt6–Wnt10* cluster is found in insects, albeit with lineage specific rearrangements, but it remains to be determined whether *Wnt5* and *Wnt7* are still clustered in any arthropods (Bolognesi et al., 2008a).

2.2. *The function of Wnt ligands in Drosophila*

The function of *Wnt* ligand genes has been most thoroughly investigated in *Drosophila*. These studies over a period of nearly 30 years illustrate the impressive range of developmental processes regulated by the seven *Drosophila Wnt* genes. Historically the *Drosophila Wnt* genes were generally named in the order in which they were discovered, rather than with respect to homology to vertebrate *Wnt* subfamilies. For example, D*Wnt3* is not a *Wnt3* homologue. Therefore for clarity we initially give both the *Drosophila* name and vertebrate name, but thereafter refer to only the vertebrate name except in the case of *wingless* (*wg*). Note that *Drosophila WntD* has been described as an 'orphan' *Wnt* gene, but it is most likely a *Wnt8* orthologue, and therefore we use the name *WntD/8* here (Bolognesi et al., 2008b; Lengfeld et al., 2009; Prud'homme et al., 2002).

2.3. *Wingless (Wnt1)*

In *Drosophila*, *wg* is best known for its role as a segment polarity gene, but this gene is involved in a wide range of processes including development of the trachea, mesoderm, CNS, eye and appendages. Although the various roles of *wg* could be subject of an entire review by themselves, here we restrict ourselves to a brief overview of the segment polarity function, the role of this gene in the nervous system, and the eye-antennal and wing imaginal discs.

In its role as a segment polarity gene, *wg* is expressed in the posterior-most cells of each parasegment abutting *engrailed* expressing cells, and thereby defines the parasegmental boundary and determines cell fate across each parasegment (Fig. 2) (Baker, 1987; Ingham et al., 1988; Martinez-Arias and Lawrence, 1985; Martizez Arias et al., 1988; Rijsewijk et al., 1987). In *wg* mutants, part of the posterior region of each parasegment is deleted and there is a mirror image duplication of the remainder, which exhibits reversed polarity (Baker, 1987; Nusslein-Volhard and Wieschaus, 1980).

Wg and Hh signalling also have antagonistic functions in the subdivision of the mesoderm, where *wg* is required for the development of the heart and somatic musculature from the posterior region of each mesodermal parasegment (Azpiazu et al., 1996).

During embryogenesis, *wg* is also expressed in the neuroblasts and their precursor cells (Baker, 1987, 1988a). In *wg* mutants, neuroblasts fail to develop (Chu-LaGraff and Doe, 1993; Hartenstein et al., 1994). Moreover, *wg* is required for the specification of