Transcriptional regulation of the
*Drosophila cyclin E* gene during development.

A thesis submitted for the degree of Doctor of Philosophy

by

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Abstract

Cell proliferation during *Drosophila* development occurs in a complex spatio-temporal pattern and is co-ordinated with differentiation. The regulation of cell proliferation is important for correct animal development and may be achieved in part by the developmentally controlled expression of cell cycle regulators. Cyclin E, a G1 cyclin, acts as a regulatory subunit of the cyclin dependent serine/threonine kinase, cdk2. The cyclin E/cdk2 complex functions during the G1 to S phase transition of the cell cycle, promoting entry into S phase. *Drosophila* Cyclin E (DMCYCE), is an important cell cycle regulator that is both necessary and sufficient for S phase during development. *Dm cycE* transcription occurs in all proliferating tissue, and ceases when cells exit from the cell cycle into G1 phase. Ectopic *Dm cycE* transcription drives cells prematurely into S phase. These results suggest that regulation of *Dm cycE* transcription is important for appropriate cell proliferation during development.

The focus of this research has been to investigate how *Dm cycE* transcription is regulated during development, as a basis for determining how developmental signals control cell proliferation during *Drosophila* development. Three approaches have been undertaken to identify cis-acting regulatory sequences that control *Dm cycE* transcription. First, by the phenotypic characterization of a set of *Dm cycE* deletion mutations, second, by analysis of a *Dm cycE* genomic rescue construct for its ability to rescue *Dm cycE* null mutants and thirdly by expression analysis of a series of *Dm cycE* promoter-lacZ reporter constructs. Results from these experiments demonstrated that *Dm cycE* transcription is under the control of a large regulatory region, containing a complex arrangement of multiple tissue specific cis-acting regulatory elements. The complexity of these cis-acting regulatory elements suggested that *Dm cycE* transcription may be regulated directly by developmental signals, providing a potential mechanism by which cell proliferation may be co-ordinated with developmental processes.

In an attempt to identify potential trans-acting regulators of *Dm cycE* transcription, research has been focused on the embryonic epidermal thoracic patch cells. This tissue is unique in the embryo, as cell proliferation appears to be regulated at the G1 to S phase transition. Analysis of *Dm cycE* transcription in several patterning gene mutants indicated that the homeobox protein Ultrabithorax is either directly or indirectly repressing *Dm cycE* transcription and that the signalling protein Wingless may positively regulate *Dm cycE* in the epidermal thoracic patches, suggesting a link between developmental patterning cues and the regulation of cell proliferation.

This research has formed the basis for the identification of transcriptional regulators that bind to *Dm cycE* cis-acting regulatory sequences. Such studies will provide insight into how developmental signals and patterning cues, control *Dm cycE* transcription and therefore cell proliferation during development.