THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Joseph C. Siefert

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Cell Biology

Friday, July 21, 2017, 2:00 pm
Biomedical Research Center, Room 109

THE ROLE OF THE DNA REPLICATION TIMING PROGRAM IN VERTEBRATE DEVELOPMENT

COMMITTEE IN CHARGE:
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ABSTRACT: The precise order in which different segments of a genome are duplicated defines the DNA replication timing program. The importance of this program is underscored by its close relationship with chromatin structure and gene regulation. Changes in the replication timing program have been observed when embryonic stem cells (ESCs) are differentiated in culture, however it is unknown what changes occur *in vivo* during development. Using zebrafish as a model of vertebrate development, we profiled replication timing genome-wide at unprecedented resolution to determine the changes occurring throughout embryogenesis. Unexpectedly, in the rapid cell cycles preceding the midblastula transition (MBT), a defined timing program was present that predicted the initial wave of zygotic transcription. Replication timing was thereafter progressively and continuously remodeled across the majority of the genome, and epigenetic changes involved in enhancer activation frequently paralleled developmental changes in replication timing. Strikingly, the long arm of chromosome 4 underwent a dramatic developmentally regulated switch to late replication during gastrulation, reminiscent of mammalian X chromosome inactivation. This study reveals that replication timing is dynamic and tightly linked to epigenetic and transcriptional changes throughout early zebrafish development. These data provide insight into the regulation and functions of replication timing and will enable further mechanistic studies.