KANSAS STATE UNIVERSITY

Division of Biology Presents:

Chromosomal Instability in Ewing Sarcoma

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Mizuki Azuma
Associate Professor
Molecular Biosciences Department
University of Kansas

Ewing sarcoma (ES) is the second most common bone cancer that develops in children. The genetic hallmark of Ewing sarcoma is the *EWSR1-FLI1* fusion gene derived from a chromosomal translocation between chromosome 22 and chromosome 11. Since the generation of *EWSR1-FLI1* accompanies the loss of one EWSR1 allele, the focus of our laboratory has been on the activities of *EWSR1-FLI1* and EWSR1. Our previous study revealed that *EWSR1-FLI1* expression and EWSR1 knockdown both induce defects in mitosis and aneuploidy (changes in DNA copy number) in both human cell and zebrafish. In addition, our previous study demonstrated that the zebrafish double mutant line carrying a mutation in the *ewsr1a* allele (homologous to human EWSR1) with heterozygous and homozygous in a *tp53* mutation background promotes tumorigenesis. Therefore, our study highlighted the importance of EWSR1 during the development of Ewing sarcoma.

Approximately half of Ewing sarcoma patients carry trisomy 8 (three copies of chromosome 8), which is associated with a poor prognosis. Therefore, we hypothesized that the presence of *EWSR1-FLI1* along with the loss of one EWSR1 allele promotes the induction of trisomy 8. To track change in the copy numbers of chromosome 8, we established a unique conditional cell line that enables both *EWSR1-FLI1* expression and EWSR1 knockdown derived from a single EWSR1 allele. Specifically, the conditional cell line is integrated with the Tet-on *EWSR1-FLI1* construct into the AAVS1 locus, and a miniAID tag was integrated at the 5'end of EWSR1 locus using the auxin-degron system. When the *EWSR1-FLI1* expression and one allele-derived EWSR1 degradation were induced simultaneously, a high incidence of trisomy 8 was induced within eight days. Contrary, there was no increase in the rate of trisomy 12, the second most common aneuploidy in Ewing sarcoma, in the same condition. Trisomy 8 is likely induced by two inhibitory mechanisms of EWSR1: haploinsufficiency of EWSR1 dues to the degradation of protein due to the loss of single EWSR1 allele, and the remaining EWSR1 proteins interact with *EWSR1-FLI1*. We propose that the combination of *EWSR1-FLI1* expression and loss of EWSR1 contributes to the induction of trisomy 8 through compromised activity of EWSR1 during mitosis.

If you would like to visit with Dr. Mizuki Azuma, please contact Dr. Katsura Asano at kasano@ksu.edu.

Coffee & snacks served preceding the seminar in Ackert Hall, Room 225