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Drosophila for Breast Cancer Research – Especially on H2AvD, H2A.Z and H2A.X

Masahiko Tanabe

Department of Breast Surgical Oncology, Kyoundo Hospital, 1-8, Kanda-Surugadai, Chiyoda-ku, Tokyo, 101-0062, Japan

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Corresponding author: Tanabe M

mtanabe-tky@umin.ac.jp

Department of Breast Surgical Oncology, Kyoundo Hospital, 1-8, Kanda Surugadai, Chiyoda-ku, Tokyo, 101-0062, Japan.

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Despite having no mammary glands, *Drosophila* is a very useful model for conducting research on molecular mechanisms as well as the regulation of transcription including epigenetic changes associated with breast cancer development. *Drosophila* has been used as one of the model systems since it was first introduced by Thomas Morgan, a pioneer in genetics for the study of heredity, in the early 20th century [1]. The complete mapping of all *Drosophila* chromosomes was completed by Dr. Morgan and his colleagues. *Drosophila* has extremely large polytene chromosomes in the salivary glands. These polytene chromosomes have enabled us to directly observe chromosomal structures and band-patterns including euchromatin and heterochromatin since the early 1960s [2,3]. Most notably, the loci involved in gene activation can be visualized as chromosome puffing [3,4]. When chromosomes including puffs are immuno-stained using antibodies against factors associated with transcription and chromatin structures such as RNA polymerase II and histones, we can evaluate the state of transcription as well as modification of histone tails which are epigenetic markers on genes of interest [4,5]. In *Drosophila*, Position-effect variegation (PEV) which is observed when a gene normally in euchromatin is juxtaposed with heterochromatin, is also a very useful phenotype for analyzing factors which can convert chromatin structures from euchromatin to heterochromatin or vice versa [6]. We can analyze the functions of chromatin modifiers in the degree of eye pigmentation, i.e., the proportions of white and red pigmentation in *Drosophila* eyes, by crossing mutant lines of interest with an original PEV line [6].

Drosophila is also a useful model for analyzing human diseases including neurodegenerative disorders, cardiovascular disease, lipid metabolism abnormalities, and various cancers [1,2]. *Drosophila* orthologs have been identified for approximately two-thirds of all human disease genes, and all major signal transduction pathways are conserved between flies and humans [1,7]. In addition, useful fly databases have been established, and numerous mutant lines are available upon request. Because of these advances, *Drosophila* has become a remarkable model for functional analyses of many human genes [2]. Taking breast cancer as an example, one protein named Taiman, a *Drosophila* protein related to AIB1 which is a steroid receptor co-activator amplified in breast cancer, was revealed to regulate invasive cell behavior using a *Drosophila* model [8]. That study raised the possibility that co-activators of the *Drosophila* ecdysone receptor and the human estrogen receptor shared essential functions across species. In this way, when it is difficult to conduct certain types of experiments with human or other mammalian systems, a model system using *Drosophila* is a potential alternative, though it requires careful adjustments, which can be among the most interesting processes in such experiments.

Recently, in the field of breast cancer research, a histone H2A variant, H2A.Z, has been attracting attention as a treatment target [9]. However, it is very difficult to analyze the molecular function of H2A.Z *in vivo* in human breast cancer cases, due to cancer heterogeneity as well as the complexity of tissue specificity in human subjects. A system using *Drosophila* can overcome these challenges.

The *Drosophila* histone variant of H2AvD is especially interesting. Although it is a homologue of human H2A.Z, it has a 'SQAY' motif, which is highly homologous with a 'SQEY' motif of human H2A.X, in its C-terminal tail, such that H2AvD has two functions, that of H2A.Z and that of H2A.X [10]. H2A.Z is mainly associated with regulation of gene expressions [11]. Nucleosomes including H2AvD were found particularly enriched immediately downstream of transcription start sites [12]. On the other hand, H2A.X is a key player in double-strand DNA (dsDNA) break repair. The serine 137 (S137) in the 'SQAY' of H2AvD, corresponding to the S139 in the 'SQEY' of H2A.X, is phosphorylated when dsDNA break occurs. Phosphorylation of S137 (H2AvD) as well as S139 (H2A.X) are critical marks of dsDNA break recognition in the dsDNA repair process [13,14]. It was also demonstrated by using *Drosophila* S2 cells that acetylation by *Drosophila* Tip60 was required for selective phospho-H2AvD exchange at DNA lesions [11,15]. Thus, H2AvD appears to have the functions of H2A.Z in transcription control as well as the function of H2A.X in the dsDNA break repair [10].

To date, key factors associated with incorporation and/or exchange of H2A.Z and H2A.X have been identified by using protein purification methods [15,16]. Recently, a nucleosome-pull down assay was conducted to identify protein partners that interact with nucleosomes containing H2A, H2A.Z and H2A.X. This is particularly worthy of mention because that report described the first systematic analysis of H2A.Z and H2A.X, resulting in numerous factors, which had not been identified by conventional methods, being newly recognized [17]. Generally, in protein purification, while factors which interact strongly or exist in great abundance in the cell are easily identified, a few key factors which interact weakly and/or are rare in the cell are difficult to identify. On the other hand, genetic screening using *Drosophila* leads to the possibility of identifying such rare but potentially significant factors. Therefore, our group combined genetic screening using the *Drosophila* phenotype and a protein purification assay, resulting the identification of novel factors, such as DRG2 and Nup107, associated with H2AvD [18]. The author's current focus encompasses making the most of the *Drosophila* system, despite working clinically as a surgical oncologist treating breast cancer.

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