Editorial

Drosophila models of cancer

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In this special edition of AIMS Genetics, we highlight the use of the genetically amenable vinegar fly, *Drosophila melanogaster*, in modeling cancer. *Drosophila* has been an important model organism for over 100 years, and has made major contributions to the discipline of cell and developmental biology by the discovery of new genes and signaling pathways. Furthermore, research using *Drosophila* has provided seminal insights into gene function, which are relevant to human health. After the sequencing of the *Drosophila* and human genomes, it has become apparent that ~ 70% of human disease genes are conserved in *Drosophila* [1]. In recent years, *Drosophila* is being used more frequently as a model for many human diseases, including cancer [2-6]. *Drosophila* presents many advantages as an *in vivo* model system for the study of cellular processes that contribute to human cancer, including the evolutionary conservation of *Drosophila* genes with mammalian genes, its lower genetic redundancy, genetic manipulability, short life cycle, easy maintenance and low research costs. In regard to the hallmarks of human cancer [7], *Drosophila* presents a suitable model for the majority of these cancer hallmarks, including continued cell proliferation, resistance to apoptosis, impaired differentiation, altered metabolism, defective innate immune response, altered cell morphology and invasion/metastasis [2,6,8-12]. Additionally, aberrant asymmetric cell division and differentiation of stem cells are contributing factors in at least some human cancers [13,14,15]. In this regard, *Drosophila* presents several systems where the interaction of genetically altered stem cells with their niche in tumorigenesis can be studied [11,16-24]. In this special edition, we present eight reviews that highlight the various ways in which *Drosophila* has been used to understand the hallmarks of cancer. In particular, these reviews cover how *Drosophila* models have revealed the involvements of signaling

pathways in tissue growth and tumorigenesis [25,26,27], how altered cell polarity or differentiation contributes to stem cell induced tumorigenesis [28,29], the understanding of invasion/metastasis mechanisms [30], cell-competition and non-cell automomous aspects of tumorigenesis [31] and the impact of chromosome instability on tumor progression [32]. Moreover, these reviews highlight different *Drosophila* systems that are used to model cancer; epithelial tissues [25,26,27,30,31,32], neural stem cells [28] and germ-line stem cells [29].

Signaling pathway perturbations have a powerful impact on the process of tumorigenesis because of the multiple targets that they control, however whether they promote or inhibit tumor growth or invasion/metastasis can be context dependent. The Notch signaling pathway, which was discovered via *Drosophila* genetics studies ~ 100 years ago, is a cell-cell interaction signaling pathway involved in tissue growth control and cell fate decisions and plays a context-dependent role in tumorigenesis [33,34]. In this special issue, Antonio Boanza and colleague highlight the function of Notch signaling during *Drosophila* development and how its deregulation leads to tumorigenesis [27].

The Hippo negative growth control pathway is a conserved signaling pathway, initially discovered in *Drosophila* [35]. The deactivation of this pathway affects the expression of cell growth, proliferation and survival genes There is accumulating evidence that deregulation of the Hippo pathway is a major player in many human cancers [36,37]. Recently, *Drosophila* studies have revealed cross-talk between the Hippo pathway and the Jun-kinase (JNK) stress response pathway, which shows context dependent effects in human cancer [38]. In this special edition, Xianjue Ma reviews the importance of the Hippo and JNK pathways, and their interactions in tissue growth and invasion/metastasis in *Drosophila* models of tumorigenesis [26].

The transcription factor and oncogene, Myc, is a central player in tissue growth control that is controlled by the Hippo and Notch pathways, as well as several other signaling pathways in *Drosophila* [39,40,41]. In this special edition, Leonie Quinn and colleagues review how research in *Drosophila* has provided insights into the regulation and function of Myc and how these studies relate to the role of Myc in human cancer [25]. Myc is also a key factor in cell competition, which is a cell surveillance mechanism that enables the detection of less-fit cells. Cell competition was initially discovered in *Drosophila*, but also has relevance to mammalian tissue homeostasis and cancer [39,41,42,43]. The removal of unfit cells involves interaction of the *Drosophila* macrophage-like cells (hemocytes), which are the cellular component of the innate immune system [8,9]. Studies in *Drosophila* have also revealed that in the repair of damaged tissue, dying cells induce compensatory proliferation of surrounding cells, which is also likely to be relevant in the response of human tumors to chemotherapy [44,45]. In this special edition, Tin Tin Su reviews how the analysis of cell-cell interactions and whole organism responses to tissue damage or genetically aberrant cells in *Drosophila* has contributed to our understanding of the interaction of a tumor with its microenvironment in human cancer [31]. Since the tumor microenvironment is emerging as a major factor in the aetiology of mammalian cancer progression [7,46-49], these studies in *Drosophila* provide new insights into the understanding of human cancer.

Stem cells play an important role in several human cancers, where altered stem cell division regulation and/or differentiation programs contribute to tumor overgrowth [13,14,15]. Two reviews in this special issue cover the important topic of stem cells in cancer in different *Drosophila* tissues [28,29]. Louise Cheng and colleagues review the literature on *Drosophila* neural stem cells and how this work is providing insight into human brain cancer [28]. Greg Somers and colleague review the germ-line stem cells of the *Drosophila* testes and ovaries and how this research is contributing to

our understanding of stem cell—somatic cell niche interactions that are relevant to human cancer [29]. These reviews highlight the importance of epigenetic regulation for stem cell maintenance, cell polarity and adhesion in the regulation of asymmetric cell division of stem cells, and the activation of various signaling pathways and transcriptional programs for the correct differentiation of stem cell progeny.

In human cancer, invasion/metastasis is estimated to result in 90% of cancer morbidity [7]; and therefore, understanding the mechanisms that promote invasive/metastatic behaviour are of great importance clinically. The epithelial to mesenchymal transition (EMT) is a key event necessary for an epithelial cell to break adhesion with the other epithelial cells and to become migratory [50]. Changes in apico-basal cell polarity and cell morphology are central to this process [51,52,53]. In this special edition, Michael Murray describes the different *Drosophila* systems used to study EMT and cell invasion/metastasis and how this research has informed human cancer biology [30]. This review highlights the importance of cell polarity, cell adhesion, actin cytoskeletal regulators and signaling pathways in promoting EMT and invasive behaviour and reveals novel molecules that might provide new therapeutic opportunities for cancer therapy.

Finally in this review series, Stephen Gregory and colleagues cover the contribution of genomic instability, particularly chromosome instability (CIN), to tumorigenesis [32]. CIN is a hallmark of many human cancers, which is driven in part by loss of the DNA damage checkpoint tumor suppressor protein, p53, which is mutated in ~ 50% of all human cancer [7,54]. However, CIN is also triggered by mutation of other cell cycle checkpoint genes, such as those involved in the spindle assembly checkpoint, which is a surveillance mechanism ensuring correct connection of chromosome kinetochores to the mitotic spindle microtubules, that occurs before the metaphase to anaphase transition is initiated [55]. Disruptions to the centrosome (microtubule organizing center (MTOC)), required for correct spindle formation, is also linked to CIN [56]. Stephen Gregory and colleagues review various *Drosophila* systems used to study CIN in tumorigenesis and emphasise how *Drosophila* models are contributing to the discovery of new avenues to specifically target cancer cells that exhibit CIN to undergo cell death [32].

Overall this review series provides a snapshot of the power of the *Drosophila* model as a genetically amenable in vivo system to study the hallmarks of cancer and reveal novel genes that have therapeutic potential for human cancer. Not specifically covered in this review series are some of the emerging areas in the *Drosophila* and mammalian cancer research fields, that of cell metabolism and autophagy in cancer development [39,57-64], and epigenetic regulation of tumorigenesis, including chromatin remodeling and histone modification [65,66,67]. Furthermore, the use of *Drosophila* as a platform for anti-cancer drug discovery is an emerging area that is likely to make a major impact clinically [62,68-76]. Undoubtedly, these new areas, as well as further research into the topics covered in this review series, will provide further advances in the application of *Drosophila* models towards the understanding and treatment of human cancer.

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Conflict of Interest

Author declares no conflicts of interest in this paper.

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