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## Authors
Arnold, Arthur P
Disteche, Christine M

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# Sexual Inequality in the Cancer Cell

**Arthur P. Arnold**[1] and **Christine M. Disteche**[2]

[1]Department of Integrative Biology & Physiology, and Laboratory of Neuroendocrinology of the Brain Research Institute, UCLA, Los Angeles, California.

[2]Departments of Pathology and Medicine, University of Washington, Seattle, Washington.

## Abstract

Investigating sex differences in cancer will improve therapy for both sexes and discover sex-specific protective mechanisms. Two recent analyses by Lopes-Ramos and colleagues and Li and colleagues point to specific gene regulatory networks and genomic alterations associated with sex differences in tumor incidence and progression. Integrating this information with emerging concepts about sex biases in the genome may help focus attention on factors that shift the odds for tumor growth.

See related articles by Li et al., p. 5527, and Lopes-Ramoset al., p. 5538.

Tumors grow in unequal landscapes in males and females. Two recent interesting analyses published in *Cancer Research* (1, 2) add to a growing list of reports that demonstrate widespread sex differences in tumor incidence, progression, molecular phenotypes, and response to treatment. Lopes-Ramos and colleagues(1) integrated information on gene regulation by transcription factors, with protein–protein interaction networks and transcriptome profiling, to achieve a novel and exciting perspective that identifies significant sex differences in gene regulation to help predict clinical outcome in colon cancer. Notably, transcription factor targeting of genes implicated in the drug metabolism pathway predicted survival in chemotherapy-treated women but not men. Li and colleagues (2) discovered sex differences in patterns of somatic mutations including point mutations and copy number changes associated with many types of cancer, which may be related to sex biases in DNA mismatch repair or microsatellite instability. This sex-biased mutation load varied between tumor types and in some cases led to inactivation of specific genes in a single sex. Both studies are well powered and show genome-wide differences in cancer types well beyond those affecting reproductive tissues.

If we are going to understand these diverse cancers, it becomes critical to figure out the reasons for the sex differences. That will help optimize treatments in both sexes and uncover possible sexbiased protective or harmful factors that might suggest new therapeutic strategies. Although some sex differences obviously stem from highly gendered human

**Corresponding Author:** Authur P. Arnold, Department of Integrative Biology & Physiology, University of California, Los Angeles, 610 Charles Young Drive South, Terasaki Building 1129, Los Angeles, CA 90095-7239, arnold@ucla.edu.

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environments (occupations, drug use, etc.), which expose males and females differently to disease risks, we can also search for fundamental biological sex differences within cells that tilt the odds for tumor growth. Because of their effects on many tissues, gonadal hormones are dominant potential sex-biasing factors. But here, we focus on the inevitable contribution of inherent sex biases in the genome.

Although more than 95% of the human genome is common to the two sexes, male and female cells have a different dose of genes on the sex chromosomes. The larger X chromosome (X) and smaller Y chromosome (Y) are evolved from an ancestral pair of autosomes. The acquisition of a dominant testis-determining gene on one autosome, the proto-Y, initiated a sequence of dramatic evolutionary changes over several hundred million years that differentiated it from its sister chromosome, the proto-X. The Y stopped recombining with most of the X, except at the pseudoautosomal region. It also gradually lost most of its genes, except for genes that evolved male-specific functions, and more widely expressed genes that were highly dosage sensitive (3). Meanwhile, on the X chromosome, the evolving 2:1 sex difference in gene dosage was a major problem because some X genes occupy critical nodes or edges in multigene networks controlling basic cellular functions (3), including those altered by neoplastic transformation. In evolutionary time, cells would not have functioned equally well in the two sexes if they had a different X to autosome (X:A) ratio, at least for genes that cooperate advantageously with autosomal genes within a limited range of stoichiometric balance (4). To reduce imbalance throughout the genome and between the sexes, compensatory processes evolved, including X inactivation to randomly shut down most of one X chromosome in each XX cell, and upregulation of expression of selected genes from the active X chromosome in both sexes to match the level of expression of disomic autosomal genes (5). Finally, the autosomes may have also adapted their expression pattern and gene content to work properly in both XX and XY cells. These adjustments of dose throughout the genome would have made XX and XY cells more similar, yet several sources of inherent inequality persisted that are likely to affect disease processes including cancer.

For some genes, sex-biased expression is directly influenced by their location on the Y or the X chromosome. If any of these genes are components of pathways altered during tumorigenesis, they could cause sex biases in cancer incidence and response to treatment. First, Y genes are only found in males, and although many of these genes are testis specific, others are expressed in many cell types. Second, mutations in oncogenes or tumor suppressor genes located on the X chromosome are dominant in males, whereas females are afforded some protection especially when the mutant allele is subject to random X inactivation. Third, X inactivation is selective and incomplete. Approximately, 25% of human X genes escape inactivation and thus are expressed from both alleles in XX cells (5), so that their expression is generally higher in females than in males. Biallelic expression of “escape from X-inactivation tumor-suppressor” (EXITS) genes may explain some of the reduced cancer incidence in females (6). Fourth, X inactivation seems to spill over into the pseudoautosomal region, so that expression of genes in this region is lower in females than in males (7). In addition to these direct effects of X and Y genes to cause sex differences, other more subtle causes of sex biases may operate.

The evolving X:A balance of gene expression in the two sexes, which leads to greater sexual equality of phenotype, masks underlying sexual bias of cellular mechanisms. The balancing is presumably driven by selection pressures that assure a male– female similarity in stoichiometric X:A ratio such that XX and XY cells both operate within the limits of proper cellular function. But any sexual equality of phenotype is only possible because XX and XY cells are each doing something different, that is, using different molecular mechanisms to adjust to the fundamental difference in their genome. XX cells have to tweak their genomic/epigenomic systems to work properly in a different way than is required in XY cells. This makes the sexual balance tentative, because any perturbation in cellular environment (e.g., caused by age, environmental toxins, and tumor-producing mutations) can affect one balancing factor and leave another unopposed, leading to a sex difference in the disease state that did not exist in healthy cells.

The tenuous and changeable male–female balance could be disrupted by various factors. High on the list would be epigenetic changes that disrupt dosage compensation mechanisms (e.g., X inactivation). Abnormal reactivation of X-linked genes has been observed in some tumors, and elimination of a long noncoding RNA, *Xist*, in blood cells causes hematologic cancer (8). Copy number changes such as loss of the X or Y chromosome, a common age-related anomaly in tumors, would differentially alter nuclear structure and heterochromatic compartments in the two sexes. Any duplication/deletion of segments on the X or Y chromosome, or on interacting autosomes (2), might upset the balance of oncogenic gene pathways differently in the two sexes. The result would be a sex difference in progression or virulence of the tumor. Particularly interesting is a set of dosage-sensitive X/Y gene pairs that have retained similar functions, even though they evolved separately. These genes often have essential functions as transcription factors and regulators of RNA splicing and translation (3), and some of them are EXITS genes often mutated in tumors (6). The latent effects of sexual inequality in the genome might be responsible for the findings of Lopes-Ramos and colleagues (1) that colon tumors have similar transcriptional profiles in the two sexes, but that sex differences emerge when one measures the impact of transcription factors within gene pathways. The sex bias in transcription factor–binding patterns could reflect the signature of sex-specific balancers, which are brought out of balance by neoplastic transformation of the cells.

A picture emerges in which specific gene pathways are spring loaded by the unequal effects of the sex chromosomes, and their balancing act, so that any disruption of those pathways triggers a sex-biased cellular response. Our understanding of the genes and genomic regions targeted by sex-biasing factors has rapidly improved in recent years. New studies reveal major conclusions and details about sex biases in gene expression in tissues and single-cell types (7), and new information is emerging on characteristics of dosage-sensitive genes that require balancing to work properly in XX and XY cells (e.g., ref. 9). We know that some important histone-modifying X genes, such as *KDM5C* and *KDM6A* (a.k.a. *UTX*), escape inactivation and are thus expressed more highly in XX than XY cells, despite partial offsetting of the sex bias by the Y partner genes (*KDM5D* and *UTY*). The targets of these histone modifiers are genome wide, but discoverable in different types of normal tissues and tumors. Together with knowledge of hormone-response elements in specific genes, this information will help build up our appreciation of the sexome, which is the aggregate of sex-

biasing effects on gene networks in multiple tissues within an organism (10). Although much has yet to be learned, it may be possible now to use prior information of the sexome, with other prior information such as on transcription factor targeting (1) and sex-biased effects of mutations (2), to understand better how sex interacts with specific gene path ways to cause disease.

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## References

1. Lopes-Ramos CM, Kuijjer ML, Fuchs C, DeMeo DL, Glass K, Quackenbush J. Gene regulatory network analysis indentifies sex-linked differences in colon cancer drug metabolism processes. Cancer Res 2018 In press.
2. Li C, Haider S, Shiah Y-J, Thai K, Boutros PC. Sex differences in cancer driver genes and biomarkers. Cancer Res 2018 In press.
3. Bellott DW, Hughes JF, Skaletsky H, Brown LG, Pyntikova T, Cho TJ, et al. Mammalian Y chromosomes retain widely expressed dosage-sensitive regulators. Nature 2014;508:494–9. [PubMed: 24759411]
4. Veitia RA, Veyrunes F, Bottani S, Birchler JA. X chromosome inactivation and active X upregulation in therian mammals: facts, questions, and hypotheses. J Mol Cell Biol 2015;7:2–11. [PubMed: 25564545]
5. Disteche CM. Dosage compensation of the sex chromosomes and autosomes. Semin Cell Dev Biol 2016;56:9–18. [PubMed: 27112542]
6. Dunford A, Weinstock DM, Savova V, Schumacher SE, Cleary JP, Yoda A, et al. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. Nat Genet 2017;49:10–6. [PubMed: 27869828]
7. Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R, et al. Landscape of X chromosome inactivation across human tissues. Nature 2017;550:244–8. [PubMed: 29022598]
8. Chaligne R, Heard E. X-chromosome inactivation in development and cancer. FEBS Lett 2014;588:2514–22. [PubMed: 24937141]
9. Naqvi S, Bellott DW, Lin KS, Page DC. Conserved microRNA targeting reveals preexisting gene dosage sensitivities that shaped amniote sex chromosome evolution. Genome Res 2018;28:474–83. [PubMed: 29449410]
10. Arnold AP, Lusis AJ. Understanding the sexome: measuring and reporting sex differences in gene systems. Endocrinol 2012;153:2551–5.