Commentary

All Damage Is Not Created Equal: Unraveling the Complexity of Sex Chromosomes and Hormones in the DNA Damage Response

Monica Venere1 and Justin D. Lathia2,3,4

1Department of Radiation Oncology, The Ohio State University, Columbus, OH, USA; 2Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; 3Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA; and 4Case Comprehensive Cancer Center, Cleveland, OH, USA

ORCID number: 0000-0003-3188-7290 (J. D. Lathia).

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Despite a growing appreciation that there are sex differences for most aspects of cancer, inspired by clear epidemiological differences in incidence, with males having an overall higher incidence and mortality for most nonreproductive cancers (1), the mechanistic underpinnings are just being appreciated. Recent evidence across multiple cancers has demonstrated clear evidence for sex differences in the genetic lesions (2) and immune response (3), but how this impacts fundamental cell biology processes is less clear. To that end, Broestl and Rubin provide a comprehensive review in a recent issue of Endocrinology that highlights variances in cellular responses to DNA damage between male and female cancer cells and link these alterations to overall patient response to therapy as well as cancer incidence (4). As the majority of nonsurgical cancer treatment interventions employ a combination of radiotherapy and chemotherapeutics that impinge on the DNA damage response, understanding inherent differences between male and female patients is paramount to improving patient outcomes. This is an immediate priority as it has recently been observed that the chemotherapeutic regimen for glioblastoma, temozolomide, is more effective in female patients (and tumor cells derived from female glioblastoma patients) that their male counterparts (2). Hence, this critical new layer of precision medicine holds the hope of ultimately providing translational targets tailored by sex.

In regards to differential cell intrinsic mechanisms, players well-known to be central to the cell fate decision following DNA damage have been implicated, namely the tumor suppressors p53 and Rb. It at first may seem surprising that there would be sex-based differences in these key, ubiquitous pathways. However, the authors highlight prior evidence in the literature in other biological contexts and studies recently reported by the authors using a unique cellular system to interrogate the role of p53 in male vs female transformed astrocytes underscore that female cells preferentially undergo the tumor suppressive cell fate choice of senescence (5). If this choice is cell intrinsic, then the next obvious question is whether sex chromosomes and/or epigenetics are involved. Here, there is compelling data linking upregulation of both p53 and Rb in female vs female transformed astrocytes underscore that female cells preferentially undergo the tumor suppressive cell fate choice of senescence (5). If this choice is cell intrinsic, then the next obvious question is whether sex chromosomes and/or epigenetics are involved. Here, there is compelling data linking upregulation of both p53 and Rb in female cells to evasion of X-inactivation by the histone lysine demethylase and proposed tumor suppressor, Kdm6a. These findings present the intriguing possibility of altering the cell fate choice of male cells by identifying therapeutic interventions that shift...
cellular responses to the more favorable pathways female cells utilize, such as those involving KDM6A.

The contribution of sex chromosomes to the differential responses to DNA damage between male and female cells is intriguing but cannot be completely decoupled from organismal level influences of sex differences on cancer incidence and response to treatment. Here, evidence is presented by the authors supporting that cell intrinsic differences are wired early on in development in a global manner during sexual differentiation. Hence, the physiological and phenotypic impact of both X and Y gene expression combined with the role of sex hormones together influence what is ultimately seen as cell intrinsic responses. This line of thought also underscores that further study of the DNA damage response during development may elucidate additional variances between males and females that may be therapeutically exploited. While this may seem complex to unravel in an experimental system, the authors highlight that the fore core genotype (FCG) model may be employed, which allows for the separation of the influence of chromosomal and gonadal sex through moving the sex-determining SRY genes from a sex chromosome to an autosome (6). While used extensively in neuroscience and behavioral studies, the FCG model has not yet been used for detailed analyses in any cancer models. The FCG mice may provide key insight into the individual contribution of sex chromosomes and hormones and their combination to DNA damage response and potential sensitivity to radiation and chemotherapy.

Ultimately, to support the translation of any identified intracellular mechanistic differences between male and female cancer cells, the relevance of these differences must be substantiated at the patient level, and the authors outline evidence well in that regard. Namely, there are population-level studies based on environmental exposure to DNA damaging agents, exposure related to cancer treatment, and cancers that are linked to germline genetic aberrations in components of DNA damage repair pathways that support higher incidence and lower survival for males. Therefore, a causal link to sex differences in the response to DNA damage is playing out on the cellular and clinical level.

As the field moves forward, the understanding of this link will only continue to grow. There is more to learn regarding influences beyond cell intrinsic DNA damage pathways and how intratumoral heterogeneity as well as tumor microenvironmental heterogeneity may feed into sex differences. These concepts are not operating in isolation and should be viewed in an integrated manner as there are clear evidence that the cancer stem cell state has an enhanced capacity to repair DNA damage (7) and that there may also be a sex bias in that cancer stem cell state, being enhanced in male tumors (5). While deep mechanistic insight into the potential sex differences in each of these fundamental cancer phenotypes is necessary, an integrative model may provide new insight into the dynamics of tumor growth and therapeutic response that may open up actionable sex-based therapeutic paradigms.

Additional Information

Correspondence: Justin D. Lathia, PhD, Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, 9500 Euclid Ave, NC10, Cleveland, OH 44195, USA. Email: lathiaj@ccf.org.

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