Bladder Cancer 9 (2023) 287–288
DOI 10.3233/BLC-239009
IOS Press

Paper Alert

Y Chromosome Loss and Bladder Cancer

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Received 9 August 2023
Accepted 28 August 2023
Pre-press 9 September 2023
Published 25 September 2023

The Y-chromosome until recently had not been regarded to be as consequential as other chromosomes in mammalian development. However, it is needed for male sex determination and spermatogenesis [1], and a variety of other functions [2]. This work has been facilitated greatly by advances in molecular genetic methodologies, particularly the development of CRISPR/Cas9- mediated knockout of parts, or all of entire chromosomes [3]. Indeed, loss of the Y chromosome (LOY) has been identified in many cancer types and as many as 10–40% of human bladder cancers [4–8]. Now a recent publication sheds some light on how LOY potentially drives cancer growth and progression and focuses on bladder cancer [9].

Abdel-Hafiz and coworkers developed a Y chromosome expression signature composed of 18 genes expressed in normal urothelium that are encoded on the Y chromosome. Using The Cancer Genome Atlas (TCGA) gene expression data and outcome from 300 male patients with muscle invasive bladder cancer where at least age, race, and tumor grade were known, they interrogated for a high or low Y expression signature, dividing the groups into Y high (N = 182) and Y low (N = 118) groups. Patients in the Y low group had significantly lower overall survival ($p = 0.029$). Then, using the mouse bladder cell line MB49, they engineered LOY (y-) or specifically knocked out 3 genes (*Kdm5d*, *Uty*, and *Ddx3y*) individually that are encoded on both the human and mouse Y (y) chromosome, as well as *Eif253y*, which is a mouse y chromosome encoded gene (not on the Human Y chromosome) normally expressed in mouse urothelium. They focused on *Uty* and *Kdm5d* whose reduced expression in the TCGA was associated with poor survival. A partial explanation for the increased aggressiveness of tumors lacking *Kdm5d*, is that human Kdm5d down regulates the expression of genes involved in tumor invasion such as matrix metalo-proteinases (MMPs), so loss of this gene will increase MMP expression and enhance cancer cell invasiveness [10]. *y*+ MB49 tumors in which either of these genes (*Kdm5d* or *Uty*) were knocked out, grew more briskly than *y*+ MB49 tumor cells expressing these genes normally when subcutaneously implanted in male wild type (wt) mice. However, growth was not affected in immunosuppressed mice (both T and B cells knocked down), implying expression of these genes augments immune responses that control (reduce) MB49 growth. Similarly, y- MB49 cells in which either *Uty* or *Kdm5d* are overexpressed, grow less vigorously than y- MB49 cells in wild type mice. To determine which part of the immune system was involved, individual B and T cell KO mice were employed and it was only in the T cell KO mice that y- MB49 cells with *Kdmd5* or *Uty* overexpressed grew as well as y- MB49 cells.

y-MB49 cells suppress immune responses in wt mice through a variety of means, but one is to increase PD-1 and PD-L1 expression (thus blocking T cells' killing of tumor cells). However, this also makes the tumors potentially more susceptible to check point inhibitor therapy, and *in vivo* tumors derived from

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y-MB49 cells have increased expression of markers of CD8 T-cell exhaustion. This was confirmed with TCGA bladder cancers with Y low expression. Moreover, growth of subcutaneously implanted y-MB49 cells in wt mice can be suppressed when treating with anti PD-1 therapy, a treatment which has no effect *in vivo* with *y*+ MB49 cells. Similarly, using data from a clinical trial (IMvigor-210) of anti PD-L1 therapy, Y low bladder cancers in patients, while more aggressive in general, are more responsive to check point inhibitors.

In summary, loss of Y chromosome genes in both human bladder cancer specimens and mouse bladder cancer cell lines, have a more aggressive phenotype, which is not only intrinsically more aggressive, but induces T-cell exhaustion and other molecular characteristics which dampen anti-tumor immunity. However, these tumors appear to have better responses to checkpoint inhibitor therapy.

The work was deemed significant enough and so well carried out, with potential clinical utility, that it was published in Nature, a rare feat for any article on bladder cancer. Despite the elegant nature of this work, it does not address a fundamental question in bladder cancer epidemiology—why men have a 3x incidence of the disease even in situations of equal carcinogen exposure (many of these studies have focused on sex hormones and their receptors) [11], or why women, who lack the Y chromosome but have paralogs for many of the genes on it, are more likely to die from bladder cancer than men [12, 13].

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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