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Short Note

The Role of The X-Chromosome Numerical Abnormalities in Cancer Development

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Abstract

Every living species has a unique set of chromosomes that carry the necessary and sufficient genetic information to survive and reproduce. In order for living organisms to reproduce, it is very important that they correctly transfer their genetic information to new generations of cells. Here, defects in DNA replication, defects in cell cycle progression and control points, repair of DNA damage, correct and balanced separation of chromosomes are important. An error in any of these genetic pathways can lead to cell death or the formation of cells with altered genetic information. Since this situation changes the expression of genetic information significantly, it causes the development of pathological defects in the embryo or organism. The numerical chromosome abnormalities (NCAs) occurring in the organism are defined as aneuploidy. Cancer-related genetic events; it is unknown how activation of oncogenes and inactivation of tumor suppressors occurs with genes on the X chromosome. The molecular basis for the oncogenic effects of doubling the copy number of the genes that are affected is also unclear. But, the X-chromosome aneusomy is thought to have a possible role in neoplastic transformation. The X-chromosome monosomy provides a unique genetic gain for the expression of common cancer-causing genetic events. In this review, we explain the unique features of X chromosome with the features of cancer biology.

INTRODUCTION

We are just beginning to understand the molecular mechanisms that damage DNA in the formation of NCAs. These abnormalities are directly related to some pathological defects and seriously affect embryo development and may be the most common cause of spontaneous abortions. Most eukaryotic organisms are diploid, meaning they have two sets of chromosomes, whereas prokaryotes are haploid, so containing a single chromosome in each cell. In human, male cells have only one X chromosome, and in XX female cells one of the X chromosomes undergoes inactivation, which silences most of the genes encoded on this chromosome. The X chromosome is a unique chromosome within the entire set of chromosomes. Sequences on the X-chromosome make up about 5% of the human genome, and carries approximately 1500 genes that are observed in human cancer cells. Cancer can be initiated by a single genetic event occurring either in somatic cells or in germ cells, leading to sporadic cancers or hereditary cancers, respectively. Although female mammals carry two copies of the X chromosome, as in females one copy of the X chromosome is inactivated, a situation that leads to specific characteristics for genes located on this chromosome. We do not know if X inactivation has any other effects other than the reasons we know. Increased dosage of X-linked genes is thought to represent a key event in oncogenesis. The main types of genetic alterations that lead to cancer tumour-suppressor inactivation and oncogene activation act dominantly when they affect the single active copy of an X-linked gene. The same alterations remain silent when they affect the inactivated X chromosome in female cells. Two principal mechanisms that achieve such change in gene dosage are commonly observed in tumours; gain of whole copies or regions of the active X-chromosome and loss or skewing of the inactivation mechanism. The expression of X-linked genes can be altered by changes in methylation. Increases and decreases in methylation of X-chromosome genes are known to play a role in some cancers. Some genes that are located on the inactive X chromosome escape inactivation in normal cells and several of these are implicated in human cancer. Defects in the X-chromosome inactivation process can also lead to cancer. However, it is known that the X chromosome carries the greatest number of immune-related genes from whole human genome [1]. To date, most studies of apocrine differentiations are based on AR expression in neoplastic cells. X chromosome gain has been previously described in male breast cancer. Androgen receptor (AR) gene is located on X chromosome. However, male breast cancer showed mainly X-chromosome polysomy and related AR gene copy number gain [2,3]. These results lead to two considerations: X-chromosome aneusomy can play a role in the neoplastic transformation of mammary epithelium and may regulate therapeutic response to molecules for anti-AR therapy.

Genetic instability is a defining feature of human cancers. NCAs are an indicator of the characteristic genetic change that occurs in the cancer genome. Aneuploidic changes are effective on cancer formation, progression and prognosis, and are frequently observed in cancer tissues and approximately 70% of all solid tumors. Given that the X chromosome carries many genes, the survival and reproduction of individuals with

X aneuploidy is thought-provoking. X chromosome numerical changes in women are known to occur more frequently than the Y chromosome changes seen in men. Genetic alterations involving the X chromosome that can lead to cancer include gains and losses of chromosomes, genomic rearrangements and mutations, which can lead to activation of oncogenes. However, the involve genes on the X chromosome are important to keep in mind the unique status of this chromosome within the chromosome set. In human, male cells have only one X chromosome, and in XX female cells one of the X chromosomes undergoes inactivation, which silences most of the genes encoded on this chromosome. Because of X-chromosome monosomy (genetic unisomy in males and functional unisomy in females), the common genetic events that cause cancer oncogene activation and tumour-suppressor inactivation are expected to produce different results. It is known that one of the detrimental effects of chromosome aneuploidies is slowing of cell growth or cell death. Interestingly, there is a relationship between apoptosis and X-chromosome monosomy. Since the gene encoding the inhibitor of the apoptosis protein is on chromosome X, the survival of the cells may be ensured by overexpressing this gene in cancer cell lines.

Aneuploidy is effective on cancer formation, progression and prognosis. Aneuploidic changes are frequently observed in cancer tissues and approximately 70% of all solid tumors, and these defects appear as autosomal and gonosomal disorders. Given that the X chromosome carries many genes, the survival and reproduction of individuals with X aneuploidy is thought-provoking. X-chromosome numerical changes in women are known to occur more frequently than the Y-chromosome changes seen in men. The researchers found that six of the 800 genes found on the X chromosome alone in 21 tumor types were mutated more frequently in women than men. Five of these genes were known to be those that escaped X chromosome inactivation [4]. Interestingly, there is a relationship between apoptosis and X-chromosome aneusomy. Since the gene encoding the inhibitor of the apoptosis protein is on chromosome X, the survival of the cells may be ensured by overexpressing this gene in cancer cell lines. Genetic alterations involving the X chromosome that can lead to cancer include gains and losses of chromosomes, genomic rearrangements and mutations, which can lead to activation of oncogenes. Can having two copies or more of the X chromosome help explain women get cancer? In other words, having two copies of the X chromosome may help explain why females get cancer less often than males, or does having two copies or more of the X chromosome protect women against cancer? Because of X chromosome monosomy (genetic unisomy in males and functional unisomy in females), the common genetic events that cause cancer oncogene activation and tumour-suppressor inactivation are expected to produce different results. Polysomy is also a condition in which an organism has one or more chromosomes than normal, meaning there may be three or more copies of the chromosome instead of the expected two. This is usually caused by non-disjunction (the failure of a pair of homologous chromosomes to separate) during cell division. Polysomy is found in many diseases, as in Down syndrome.

It is also known that aneuploidy is an independent diagnostic factor in breast and colorectal carcinomas that increases in accordance with the cancer stage. Also, many environmental, genetic and epigenetic factors have been reported to affect the pathogenesis of breast cancer (BC). BC is the leading cause of cancer deaths in women, affecting 2.1 million women each year. Aneuploidy is a defining feature of BC but rarely been studied in breast carcinogenesis. Related to this, it has been reported that the numerical sex chromosamal abnormalities (NSCAs) increases in relation to the progression of the disease in breast and gonadal cancers [5-7]. We have reported NSCAs very frequently in our studies with breast cancer, lung cancer, bladder cancer, hematological malignancies and pleomorphic sarcoma [8-16]. In a recent study we conducted in female patients with breast cancer (BC), NSCAs in cancer tissues were investigated and their relationship with clinical and biological data by fluorescent in situ hybridization (FISH) technique [17]. We found that X-chromosome polysomies increased in BC patients with raised age (p=0.020) and who breastfeeding their children (0.039) and an increase of X-monosomies who give a son at first pregnancy (p=0.016). On the other hand, X-monosomies was higher in the early stages (I and II) than in the advanced stage (III and IV) and the difference was statistically significant (p=0.020). These findings showed that the rate of X monosomy is high in patients who gave birth to boys in the first pregnancy, the rate of X polysomy is high in breastfeeding patients, and the rate of X monosomy in the early stages of cancer but the X polysomy ratio was low. Here, it is remarkable that monosomy X in the early stages of BC and polysomy X in the late stages was significantly higher. However, It appears that polysome X, advanced age and breastfeeding have possible roles in the biological behavior of grade III tumors. The similarities of losses involving chromosomes X in malignant breast lesions suggest that some hyperplasias may be part of a sequence of progression to malignancy in BC. However, polysomy of chromosomes X was present as the predominant alteration in phenotypically aggressive breast cancer tumors, whereas gain of chromosome X, in particular, is probably implicated in cell survival. This indicates that X-chromosome loss may cause an early event in breast carcinogenesis. However, It appears that polysome X, advanced age and breastfeeding have possible roles in the biological behavior of grade III tumors. To verify this, new studies should be conducted in relation to clinical features.

In particular, normal human cells rarely have monosomy while generally cancerous cells show a monosomic structure. Indeed, the loss of X chromosome seen in the early stages of cancer tissue in our patients with breast cancer confirms this [17]. In other words, we can say that the genes found on the X chromosome at the beginning of cancer formation are caused by haplo deficiency. Often, it can be thought that other numerical and structural chromosomal aberrations in addition to the monosome in cancer cells are accompanied and haplo-deficiency compensated by these genomic changes. Not all tissues are equally susceptible to cancer formation associated with NCA. Changes in gene expression levels other than gene mutations that impair protein function can also lead to aneuploidy and cancer formation. All these findings; It reveals that NCA and chromosome instabilities facilitate cancer formation. In addition, there is limited information about the effects of NCA on gene expression in some eukaryotic organisms. On the other hand, it is known that cancer cells acquire immortal characteristics require the formation of multiple mutations in various genes that cause

proliferation. Approximately 75% of hematopoietic cancers and 90% of solid cancers carry cells with NCA [18]. Recent comprehensive findings; It is known that somatic copy number changes in human cancers are affected by the whole genome or whole chromosome copy number changes in approximately one quarter of the cells. Many of these are not random changes, but it is accepted that this is the result of genetic preferences of cancer types.

Our results also confirm that the absence of an X chromosome may play a role in cancers. On the other hand, the gain of a X chromosome is common in leukemias, lymphomas, and prostate cancer and usually occurs in association with other karyotypic changes. The reason for this is generally unknown. At the same time, it is not also known whether this gain is due to the active or inactive X chromosome. There are many X-linked genes in the neoplasia that may be located in the pseudo-autosomal region and in other regions, possibly escaping X-chromosome inactivation. Increases of chromosomes X were associated with aggressive features of breast tumours such as advanced stage, larger tumour size, as has already been mentioned for in situ and invasive ductal carcinomas of the breast [19]. In a study, polysomy of 16 and X chromosomes was detected as the dominant abnormality in patients with BC (73.7% and 57.9%, respectively). X-chromosome polysomy was also found to increase in high grade ductal carcinomas and high nuclear grade tumors [20]. In addition, over-representation of chromosome X has been related to lymph node involvement in breast cancer, and constitutes a recurrent change in non-Hodgkin's lymphoma and in meningioma tumours in both female and male patients, whereas loss of the X chromosome is observed in invasive ovarian carcinomas [21-24].

Among the diseases that show X-chromosome numerical aberrations; The Turner phenotype is the result of one of the most common cytogenetic abnormalities, is characterised by complete or partial X-chromosome monosomy. It is known that the risk of solid tumors is increased in people with Turner syndrome, but the reason for this has not been determined. In addition to the increased risk of gonadoblastoma, it suggests that women with Turner syndrome appear at increased risk for meningioma and childhood brain tumors, and possibly bladder cancer, melanoma, and corpus uteri cancer, but are at risk for breast cancer [25]. Reasons for these risks might relate to genetic and hormonal factors or to the effects of hormonal treatments given to women with Turner syndrome. Long-term hormonal treatments given during the premenopausal age range seems not to exert a cancerous effect in Turner syndrome. The decreased risk of breast cancer was in line with the etiology of estrogen contribution on most of breast cancer, as women with Turner syndrome have low concentration of estrogen in the body. The findings support that the X chromosome may play an important role in the incidence of solid tumors, as shown by increased risk in women with Turner syndrome and reduced risk in men with Klinefelter syndrome.

However, the risk of solid and hematological malignancy in patients with Turner syndrome, characterized by X-chromosome monosomy in women and characterized with two and more X chromosomes in men (Klinefelter syndrome) is not well established. Some studies support the hypothesis that the X chromosome plays an important role in solid tumor etiology [26]. It is known that androgen receptor gene mutations exist in men with breast cancer and that this gene escapes X-chromosome inactivation. In an our study, it was reported that the most common karyotype among NSCAs in male breast cancer tissue was 48,XXYY (31.7%) [10]. It has been reported that a suppressor gene on the Y chromosome is responsible for cancer development at an early stage, and some genes on the Y chromosome are involved in cell cycle regulation, signal transmission, cellular growth, protein destruction, and gene expression [27]. For these reasons, it can be suggested that a mutation that may occur in these genes may cause cancer. These results suggest that some gene(s) on X or Y chromosomes that are increased in peomorphic sarcoma escaped X-inactivation and may be highly expressed. As a matter of fact, it is known that the risk of having breast carcinoma increases relatively in men with 47,XXY syndrome (Klinefelter syndrome).

Although the mechanism is unknown, it has also been suggested that the putative role of X chromosome disorders in solid tumor etiology may also be associated with loss or dysfunction of immune-related genes [26]. Given that the X chromosome harbors important cell differentiation and proliferation genes-as well as cancer-related genes-genetic changes occurring on vulnerable sex chromosomes may cause immediate damage, moreover, such mutated cells are more likely to develop into tumor cells in the genetic process [28]. However, it is assumed that a few genes on the X chromosome that protect against cancer may escape this inactivation. These X-inactivation tumor suppressor genes were called "exit-escape genes". Xist region on X chromosome is a key regulator of dosage compensation that randomly inactivates an X chromosome in a during embryonic development. Xist-led X chromosome inactivation processes silence hundreds of genes (including oncogenes); therefore, the loss of Xist expression promotes tumor development [29]. It is known that genes with more frequent mutations in males are found only on the X chromosome, and many of these are tumor suppressors and escape X-inactivation. Based on the evidence described above, we can speculate that women with Turner syndrome may experience an increased risk of solid tumors as immune system dysfunction plays an important role in their etiology. On the contrary, for men with Klinefelter syndrome the extra copy of X chromosome may protect against the loss of immune-related genes located, and they may face a lower or similar incidence of solid tumors as compared to healthy men. It is necessary to determine whether the active or inactive X chromosome is involved in the loss of heterozygosity, in which multiple X-linked genes that escape X chromosome inactivation are potentially involved in cancer, and it will be necessary to define these genes and their roles in different cancers.

Lung cancer (LC) is one of the leading causes of cancer deaths in the world. Chromosome irregularities in LC can provide useful findings in identifying the relevant target loci and responsible genes. In a study we conducted with LC patients, NCAs were seen in approximately 67% of cancer tissue cells of patients [16]. The most common numerical irregularities; It was found to occur on 1, 3, 5, 6, 9, 11, 17, X and Y chromosomes. Among these chromosome irregularities, it was observed that autosomal

monosomes were leading, followed by numerical abnormalities of X and Y chromosomes. Bladder cancer is a heterogeneous group of tumors from both the biological and clinical points of view. High polysomies of certain chromosomes have been reported in bladder tumor groups [30]. At the same time, in patients with bladder cancer, X-chromosome polysomies were observed in 71.4% of the cases, while numerical aberrations of the Y chromosome were observed in 62.9% of the cases. Here, it was reported that there was a possible correlation between X or Y-aneusomies and tumor grade [31]. In a study we conducted with patients with bladder cancer, we commonly reported abnormalities in the sex chromosome and autosomal monosomes (X, Y, 22, 21, 17 and 8 chromosomes) [12]. These findings are; It shows that numerical chromosome irregularities, especially the X and Y chromosomes may play a role in the progression of cancer.

CONCLUSION

The X-chromosome monosome may be a clear genetic marker for the expression of inactivation of common cancer-causing genetic events (i.e., oncogene activation and tumor suppressor). Because females have two X chromosomes, they might be expected to be less susceptible to mutations in tumour-suppressor genes. As previously suggested, the silent copy of the X chromosome can mask oncogenic events and make female cells resistant to events that promote early cancer [32,33]. The conclusion that can be drawn from all studies is that gene dosage seems to be a central mechanism in the oncogenic processes that are linked to X-chromosome alterations. The molecular basis for oncogenic effects of affected genes is unclear. The expression profiles of X-linked genes in tumor cells should aid in understanding how events associated with the X chromosome lead to oncogenesis, which will provide useful information for diagnosis internal and prognostic purposes.

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