Organisms
Journal of Biological Sciences

Vol. 1, 1 (JUNE 2017)
ISSN: 2532-5876
DOI: 10.13133/2532-5876_1.10
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ORIGINAL ARTICLE

A critical re-examination of the role of chromosome translocations in cancer

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Abstract

A chromosome translocation occurs at random in many hematological and solid malignancies and is considered the initiating event of carcinogenesis. However, the early events of carcinogenesis do not entirely align with this hypothesis. First, chromosome translocations are observed more frequently than expected if they were truly a random event. Second, chromosome translocations are often found in healthy individuals, and a specific rearrangement may be observed in up to half of the general population. Third, tissue proliferation is observed before chromosome translocation. Further, the at-random breakage–re-ligation–selection mechanism proposed to explain chromosome translocations in cancer is not well understood, particularly regarding how chromosomes come in contact with each other. These observations open the possibility that an alternative mechanism may contribute. Here, a model is proposed to describe how chromosome translocations, which are often observed in stressed tissue, could be produced in relation to transcription. Transcription–associated recombination may explain how over-expressed genes that are temporally in close proximity may become abnormally fused. This model offers a framework for the hypothesis that early carcinogenesis promotes chromosome translocation, rather than that cancer is initiated by chromosome translocation. Further, the hypothesis suggests that the role of genetic modifications observed early in malignancy is more complex and less determining than currently considered and implies that therapy targeting genetic modifications could miss the causal mechanism.

Keywords: cancer and chance, carcinogenesis, chromosome translocation, transcription, transcription-associated recombination

Citation: Satgé, D, 2017, "A critical re-examination of the role of chromosome translocations in cancer", *Organisms. Journal of Biological Sciences*, vol. 1, no. 1, pp. 53 - 60. DOI: 10.13133/2532-5876_1.10.

This text is dedicated to the memory of Doctor Jean-Louis Wuyts.

1. Introduction

Chromosome translocations, the rearrangement of genetic material between non-homologous chromosomes, are observed in all types of malignant disorders: hematological malignancies, sarcomas, and carcinomas. In fact, translocations were the first consistent genetic modification identified in human cancer (Nowell and Hungerford 1960). This discovery led to the idea that chromosomal and genetic anomalies play important roles in the initiation of carcinogenesis by providing proliferative advantages to cell clones (Nowell 1976, Greaves and Wiemels 2003, Mitelman et al 2007). Translocations exert effects on cell phenotype by inducing over-expression of a gene situated close to the breakpoint or by creating a fusion gene. However, how and when chromosome translocations occur in the nucleus remains unclear, and the significance of chromosome translocations during tumorigenesis remains poorly understood (Mitelman et al 2007, Mathas 2009, Roukos 2013).

The somatic mutation theory of cancer (SMT) proposes that translocations are significant contributors to

the early steps of carcinogenesis. This paper presents an alternative hypothesis based on several observations that do not support the SMT. Instead of at-random breakages followed by re-ligation and clone selection, this new hypothesis suggests that chromosome translocations occur at over-expressed genes through transcription–associated recombination. Importantly, therapeutic strategies based on the paradigm that cancer is a genetic disease have not been as successful as hoped (André et al 2014, Le Tourneau et al 2015). Therefore, a better understanding of the pathogenesis and role of early molecular modifications in cancer tissues is critical to advancing therapeutic options.

2. Reconsidering the somatic mutation model of cancer

2.1. Translocations occur too frequently to be random events

In the framework of the SMT, a specific chromosome translocation is considered specific to a given tumor during tumor progression. The theory suggests that (rare) initiating translocation events occur at random during chromosome replication. However, well-defined chromosome translocations in cancer cells are found at a higher frequency than expected from the basal human rate of chromosome translocations. For example, in the developing embryo and fetus, the frequency of *de novo* translocations has been estimated to be between five and eight in every 10,000 pregnancies (Giardino et al 2009). In contrast, the frequency of translocation in cancers is much higher; this contradicts the idea that they are random events. Similarly, the true nature of randomness is challenged by the regular production of a typical fusion gene by a prostate cancer cell line exposed to androgens and radiation (Holzman 2010).

The randomness of translocations has also been challenged by the observation of a young girl who presented two Ewing sarcomas, one of the atlas bone, the other—five years later—of the right humerus. These tumors had different *EWS* fusion transcripts: *EWS*/*ERG* [t(11;22)] for the first and *EWS*/*FLI1* [t(21;22)] for the second (Bielack et al 2004). The authors proposed that *EWS* translocation could not be the first step in the evolution of Ewing sarcoma. The presence of multiple fusion transcripts in cases of Ewing sarcoma could result from alternative mRNA splicing (Patócs et al 2013). However, this case suggests that at least some *EWS* fusion transcripts of Ewing sarcoma are favored by a kind of predisposing state. The phenomenon is similarly observed in hematopoietic tumors. Six primary cutaneous marginal zone B-cell lymphomas from four patients exhibited two different translocations in the same lesion. The first was a t(14;18) (q32;q21) *IGH*/*MALT1* translocation, bringing into proximity the heavy chain locus (*IGH* gene) and the mucosa–lymphoid tissue locus (*MALT1* gene). The second was a t(14;18) (q32;q21) *IGH*/*BCL2* translocation, bringing into proximity *IGH* and B-cell lymphoma 2 (*BCL2)* genes (Palmedo et al 2007). Different translocations involving the *MYC* and *BCL6* genes have also been reported in B-cell lymphomas (Choi et al 2011). Moreover, separate translocations can occur *in utero* and be present at birth, as found in a neonate with acute myeloid leukemia associated with both t(18;16) and t(17;19) chromosomal translocations (Sung et al 2010).

Such observations indicate that initial chromosome translocations observed in cancer occur in somatic cells more frequently than expected by chance alone. It follows that non-random translocations must therefore be preferentially produced by some underlying process. Indeed, chromosome translocations are more likely the genetic response to a particular situation, than the initiating event of carcinogenesis.

2.2. Translocations are observed in healthy individuals

Certain chromosome translocations are observed frequently in specific cancers and are therefore considered to initiate tumorigenesis in line with the SMT. However, these same translocations are also frequently found in circulating lymphocytes of healthy individuals and of individuals with non-neoplastic diseases (for a review, see Janz et al 2003). The phenomenon was first described more than 25 years ago, in the case of the t(14;18) (q32;q21) translocation found in 13 out of 24 (54%) individuals with lymphoid hyperplasia (Limpens et al 1995). Similarly, the t(14;18) translocation, one of the most common genetic aberrations in lymphoid malignancies, was found in mononuclear cells of the blood of 327/715 (46%) healthy individuals aged 0-91 years (Schüler et al 2009). Thirty-one healthy individuals even had multiple translocations. Importantly, some healthy individuals had a greater number of circulating white blood cells with a translocation than did patients with lymphoma. If one of these translocations is causing lymphoma, as predicted by the SMT, nearly half of the general population would be expected to develop a lymphoma. Yet, there is no evidence for such a phenomenon.

Indeed, the follow-up of a healthy blood donor who carried four clones of the t(14;18) translocation showed no hematopoietic malignancy over a period of six years (Dölken et al 1996). The t(3;14) (q27;32) translocation that produces an *IGH/BCL6* fusion transcript that is observed in diffuse large B-cell lymphoma and in follicular lymphoma was detected in 39/40 (96%) normal tonsils and 3/3 (100%) human spleens from healthy individuals (Yang et al 2006). The translocation t(2;5), which characterizes some cutaneous lymphoproliferative disorders, has been observed in the inflammatory non-neoplastic cutaneous disease, eczema (Beylot-Barry et al 1998). Other specific translocations, including t(9;22), t(12;21), t(8;21), t(4;11), and t(15;17) have been observed in lymphocytes of individuals without leukemia or lymphoma (reviewed by Janz et al 2003). These translocations should therefore be considered as being frequently associated with, rather than causing, hematopoietic malignancies. Moreover, these observations provide support that chromosome translocations are not cancer-specific.

2.3. Additional discrepancies in time, lineage, and causality

Two decades ago, Rowley noticed that the appearance of the characteristic t(9;22) translocation associated with chronic myelocytic leukemia (CML) was preceded by enhanced proliferation of this abnormal cell population (Rowley 1984). Similarly, the LNCaP prostate carcinoma cell line produces a typical *TMPRSSZ-ERG* fusion transcript following radiation exposure or the addition of etoposide or doxorubicin in the culture medium (Lin et al 2009). Since LNCaP cells are already malignant, the translocation can hardly be seen as the initiating and determining event. These two examples suggest that the chromosome rearrangement follows some previous modification(s) in cells that are already undergoing oncogenic transformation. Conversely, the translocation cannot be considered as a decisive event in the development of leukemia since it is observed *in utero* more than a decade before the onset of some childhood leukemias (Greaves and Wiemels 2003). In light of translocations observed in blood cells of cancer-free individuals, it is difficult to understand how such particular and frequent events induce malignancy. Consider that a group of 12 HIV-positive men exhibited the t(8;14) translocation, but only one of them developed a lymphoma after nine years of follow-up. In this patient, the tumor was negative for the translocation. Further, in the same patient cohort, only one of 12 patients with a lymphoma had the t(8;14) translocation (Müller et al 1995).

In addition to this lack of clear correspondence in temporality and causation, there are also discrepancies in cell lineage. The t(18;21) translocation, believed to induce CML, is detected in non-malignant blood lymphocytes of affected patients (Smith et al 1998). Similarly, the t(9;22) translocation was found in erythroid cells of a man treated for CML (Rastrick et al 1968). A translocation t(2;3) (q13;p25) corresponding to the fusion gene *PAX8-PPARG1* has been found in thyroid follicular adenomas (Zhang and Oliveira 2010). Additionally, between 0 and 29 chromosome translocations were detected in eight primary breast cancers (Stephens et al 2009). Together, these data challenge the relevance of the SMT and suggest that the role that chromosome translocations play during oncogenesis warrants further attention.

2.4. A debatable mechanism: at random breaks–re-ligation–selection

Chromosome translocations in cancers are proposed to occur through inappropriate re-ligation of two DNA double-strand breaks (DSBs) in heterologous chromosomes (Byrne et al 2014). The translocation would provide a survival advantage to the clone, which then proliferates (Bunting and Nussenzweig 2013). In this multistep process (Roukos and Misteli 2014) the initial event is the simultaneous occurrence of random DSBs in several chromosomes, spontaneously or through replication errors, endogenous stress, or exogenous stress. Following this DNA damage, the cells activate complex DNA repair mechanisms, particularly the non-homologous end-joining pathway (NHEJ), which may inadvertently produce translocations (Bunting and Nussenzweig 2013). There exists general agreement for this sequence of events, but their temporal and spatial aspects remain largely unknown (Mitelman et al 2007, Byrne et al 2014, Roukos and Misteli 2014).

Importantly, however, this proposal has several weaknesses. First, the responsible event, either endogenous or exogenous, that leads to DSBs would damage the whole genome at random, but the model does not account for the specific translocations that are observed in cancers. If random DSBs result in specific translocations, then it follows that millions of other chromosome anomalies and mutations would also result. Such an event has not been observed and is highly unlikely since it would be incompatible with life.

Second, the process of selection for the translocation is debated. In a model of prostate cancer, chromosome translocations were shown to be site-specific rather than produced by proliferative selection (Lin et al 2009). Oxidative stress and free radical production are also proposed as mechanisms through which DSBs are introduced. However, the role of reactive oxygen species (ROS) and of reactive nitrogen species (RNS) is unclear since inhibition of ROS and RNS did not reduce chromosome breakages in an experiment using *Helicobacter pylori* infection (Toller et al 2011). Additionally, conditions associated with DNA and chromosome instability should theoretically present malignancies with numerous fusion genes. In contrast, gene fusions are very rare in ataxia telangiectasia, Fanconi anemia, Bloom syndrome, and Nijmegen breakage syndrome, all of which are diseases associated with DNA repair anomalies (Mitelman et al 2007).

Third, despite the absence of mutagenic properties in dioxin, exposure to this pollutant leads to an increased number of circulating t(14;18) positive cells in healthy subjects (Baccarelli et al 2006). This suggests that translocation is not always the result of direct DNA damage. Fourth, the production of DSBs is proposed to generate cancer by increasing the frequency of chromosome translocations. Yet, some of the most effective cancer therapies carry the risk of increasing DSBs (Byrne et al 2014). Thus, it would be expected that these chemical agents would initiate new cancers. Considering these facts, the proposition that chromosome translocations in cancer are due to an at-random breaks–re-ligation–selection process remains controversial based on evidence collected among humans.

3. The hypothesis

3.1. Chromosome translocation as a response to tissue stress

Reactive tissues, viral infections, increased hormone levels, and abnormal exogenous exposures are examples of stressors that can enable chromosome translocations, as well as other chromosomal anomalies in individuals without malignancies. Examples of this phenomenon have been described. First, non-random cytogenetic anomalies, including chromosome translocation associated with lymphomas, are observed in reactive lymphoid hyperplasia (Sevilla et al 2011, Montgomery et al 2013). These cases indicate that cells carrying chromosome translocations may reside in non-neoplastic tissues. Second, the t(14;18) translocation is observed in HIV- and HCV-infected patients and is sometimes even undetectable after successful antiviral treatment (Molina et al 1996, Sasso et al 2004). Third, infants were found to be at increased risk of acute leukemias, particularly leukemias associated with *MLL* gene translocation, after maternal hormone use during pregnancy (Pombo-de-Oliveira et al 2006). Additionally, *in vitro* exposure of the TK6 lymphoblastoid cell line to physiological levels of estradiol increased the frequency of *MLL* translocations (Schnyder et al 2009). *In utero* exposure to the pesticide propoxur has been linked to a two-fold higher incidence of the t(8;21) (q22;q22) translocation in newborns (Lafiura et al 2007). Even dietary components—for example, flavonoids, through their topoisomerase II-inhibiting effect—induce an excess of chromosome translocations with rearrangements of the *MLL* gene when added to cord blood CD34 mononuclear cells *in vitro* (Barjesteh van Waalwijk van Doorn-Khosrovani et al 2007). These and other reports suggest that tissue stress may produce, as early as the fetal period, precise non-random chromosome translocations that are commonly found in leukemia and lymphoma in individuals without malignancies. Thus, translocations may reflect a sign of significant stress recorded in the genome (DNA sequence) of cells in an affected tissue.

3.2. A link between chromosome translocations and transcription: TAR

A correlation between gene over-expression and chromosome abnormalities like translocations has repeatedly been observed in various species including humans (Aguilera and Gómez-González 2008). A gastric cell line infected with *Helicobacter pylori* bacteria exhibited frequent chromosomal aberrations and gene mutations specific to gastric carcinoma in actively transcribed genes (Myllykangas et al 2004). The transcriptional activation of an androgen-responsive prostate cancer cell line produced chromosome translocations when exposed to d*ihydrotestosterone* (DHT), which induced transcriptional activation of androgen responsive-genes (Lin et al 2009). Similarly, B cells revealed translocation breakpoints close to the start sites of active genes (Klein et al 2011, Chiarle et al 2011). In T cells, up-regulation of genes in close proximity to the breakpoints has been documented before the occurrence of the t(2;5) translocation associated with anaplastic large-cell lymphoma (Mathas et al 2009).

Importantly, chromosome translocations occur in particular nuclear territories, identified as transcription factories (Fraser and Bickmore 2007, Osborne 2014). Genes involved in translocations are associated with transcription factories; they may naturally be found in a similar position in the nucleus of normal cells, or may be placed in close proximity by transcriptional activation (Mani et al 2009, Osborne 2014). This physical proximity suggests that chromosome translocations could occur at the time of gene transcription (Roukos and Misteli 2014). Indeed, chromosome translocations could thus be the abnormal product of over-stimulated transcriptional machinery, including the participation of mechanical forces required in the opening of chromatin structure to allow the machinery to access DNA. This over-stimulation could, in turn, result from the well-established phenomenon of transcription-associated recombination (TAR) (Aguilera 2002, Aguilera and Gómez-González 2008). In normal and basal conditions, transcription produces rare chromosome translocations that can be eliminated by cellular machinery. When transcription is increased, the clearing process is overwhelmed by the saturation of cellular repair capacity, and an abnormal gene fusion may result. A tissue exposed to stress conditions responds by activating certain genes to balance the disturbed mechanism. For instance, when cells receive an abnormal stimulation to proliferate, two genes that are involved in proliferation control may be activated in a transcription factory to correct this anomaly. These two genes may thereby be susceptible to translocation. This explains why translocations do not occur at random but on specific genes in particular tissues and under defined conditions. In this context, a translocation does not initiate the carcinogenic process, but is the mark of cellular reactions to tissue stress. The impact will differ between cell types, according to the precise physiological state at the time of the stress (Shav-Tal et al 2006).

3.3. Is cancer a genetic disease?

Let us consider that chromosome translocations found in cancers are not the initiating event but rather the cellular response to stress. These genetic modifications, then, do not necessarily play a role during subsequent steps of cancer development. Conversely, this does not imply that chromosome translocation plays no role in the process of tumorigenesis when it occurs. Nonetheless, their determining role is challenged by important observations. The NIH3T3 fibroblast cell line fails to be transformed by chromosomal translocation-activated genes, indicating a specificity for a cell type rather than for cancer in general (Rabbitts et al 1999). Further, only 5-15% of mice transgenic for t(14;18) develop a high-grade malignant lymphoma after a long latency (McDonnell and Korsmeyer 1991), and the presence or absence of a t(11;18) translocation does not modify the response to chemotherapy (Streubel et al 2004). Indeed, the over-expression of genes commonly involved in a translocation can occur in patients with tumors but without the translocation. For instance, the BCL2 anti-apoptotic protein favoring survival and expansion of clonal B cells is over-expressed in patients who do not have the t(14;18) translocation (Witkowska and Smolewski 2013). *FRA2*, *ID2*, and *CSFR1* genes, which map near the t(2;5) translocation, are over-expressed in the absence of the translocation in anaplastic large-cell lymphoma cell lines; non-anaplastic large-cell lymphoma cell lines do not over-express these genes (Mathas et al 2009). Such genes may play a role in a translocation-independent fashion. In summary, data collected from animal models and from human malignancies challenge the determining role of chromosome translocations in the neoplastic process.

A detailed follow-up of early biological and molecular modifications in leukemogenesis in Down syndrome revealed that mutations in the *GATA1* gene are not the initial event in the neoplastic process, but appear as a tissue response to an unbalanced differentiation–proliferation process (Satgé et al 2014). This phenomenon occurs in only one type of cancer within a defined genetic condition and is therefore unique. However, cancer has long been suggested to produce mutations rather than being the consequence of mutations (Prehn 1994). For example, many somatic mutations considered to be cancer-specific have been shown to accumulate in physiologically normal skin and in benign cutaneous tumors (Martincorena et al 2015). The data on chromosomal translocations must be added to the increasing body of discrepancies in the SMT (Bizzarri et al 2008, Satgé 2013). Alternative models of carcinogenesis that consider the cell-microenvironment interplay, such as the tissue organization field theory (TOFT), are emerging, producing new hope for therapeutic approaches (Sonnenschein and Soto 2008, Baker et al 2010, Soto and Sonnenschein 2014, Bizzarri and Cucina 2014). They deserve attention, particularly when the architects of the SMT (Hanahan and Weinberg RA 2000, Hanahan and Weinberg RA 2011) acknowledge that the SMT cannot assimilate and interpret most of the accumulated data (Weinberg 2014).

4. Conclusion

Accumulated data on the very early events of oncogenesis suggest that chromosome translocations observed in cancer are not random events. Instead, they appear in response to a tissue stress that subsequently affects physiological processes. This idea supports what is known about exogenous carcinogenic agents, and the mechanism of translocation-associated recombination is a good candidate to explain the correlation between gene over-expression and translocation. Further, it clarifies the break–re-ligation sequence, a phenomenon not well understood in the frame of the at-random breaks–re-ligation–selection model. Whatever the mechanism, translocations are unlikely to be the initiating event in oncogenesis. This raises a major question: namely, is cancer a genetic disease?

Acknowledgments

I am thankful to Professor Jean-Bernard Dubois for his comments on the manuscript and to Christiane Satgé for her assistance with the preparation of the manuscript.

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