LOSS OR GAIN OF CHROMOSOMAL MATERIAL GENERATES CANCEROUS PHENOTYPES: A REVIEW

[1]Aruomaren, A. I., and [1]Obazelu, P. A.

[1]Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin.

Corresponding Author: Aruomaren Austin Iroghama

Email: iroghama.aruomaren@uniben.edu; Phone number: +2348035238969

Received: 16th Oct., 2021 **Accepted:** 8th December, 2021 **Published:** 31st December, 2021

ABSTRACT

Background: The loss or gain of chromosomal materials is centre to the development of malignant transformations of most cells.

Aim: The purpose of this review was to search relevant literatures to determine if loss or gain of whole chromosome or chromosomal materials had better prognosis.

Methodology: In writing this review, information was searched from relevant databases such as PubMed, Science Direct, Google scholar and Medline search. Using keywords such as chromosomal aberration, tumorigenesis, cytogenetic and karyotyping.

Results: Chromosomal loss has been associated with loss of centromere integrity and aberrant merotelic attachments. Chromosomal segregation error at mitosis usually result in aneuploidy and a subsequent DNA double strand break directly result in an unbalanced translocation in the daughter cells. Whole chromosome gains are the more likely type of chromosomal aberration seen in cancer cells and this may be as a result of spindle polarity and cytokinesis failure. It thus appears that gain of chromosomal material seem to be vital for tumour progression and metastasis. Although in some other cancers like colorectal cancer, a deletion in a key chromosome could be vital in cancer tumorigenesis.

Conclusion: Loss or gain of a chromosomal material or a structural chromosome aberration could be seen as been favourable for one tumour and in contrast represent a poor prognosis for another.

Keywords: cytogenesis, tumour, chromosome

INTRODUCTION

Malignant transformation within the human cancer genomes (gain or loss of genomic materials) is usually associated with chromosomal instability (Djos *et al.*, 2013) when compared to normal cells. Aging has become a risk factor in the development of cancer, thus presenting multiple rate limiting steps in cancer development involving genetic changes (Beckman and Loeb, 2005). Gametes and somatic cells may accumulate mutation over time and this may interfere with certain cellular functions such as DNA repair and maintenance, cell cycle and mitotic checkpoints regulation (Jefford and Irminger–Finger, 2006). Cytogenetic analysis of most solid tumour, usually show aneuploidy karyotype (altered chromosome numbers and structure), however tumour development is usually linked to genetic mutation. Figure 1 below shows how changes in somatic cells, abnormal cells among other factors can affect the development of cancer which hinges on alteration in the genome. This instability in the genome usually occur through nucleotide alteration due to dysfunction in the DNA repair pathways and could result in loss or gain of chromosomal materials through chromosomal instability which is a common feature in tumorigenesis (Jefford and Irminger–Finger, 2006). However, it is still unclear how cancer cells respond to gain or loss of chromosome with recent study showing tolerance of malignant cells to chromosomal aberration. In most cancers, aneuploidy tolerance preceded cancer tumorigenesis (Valind *et al.*, 2013).

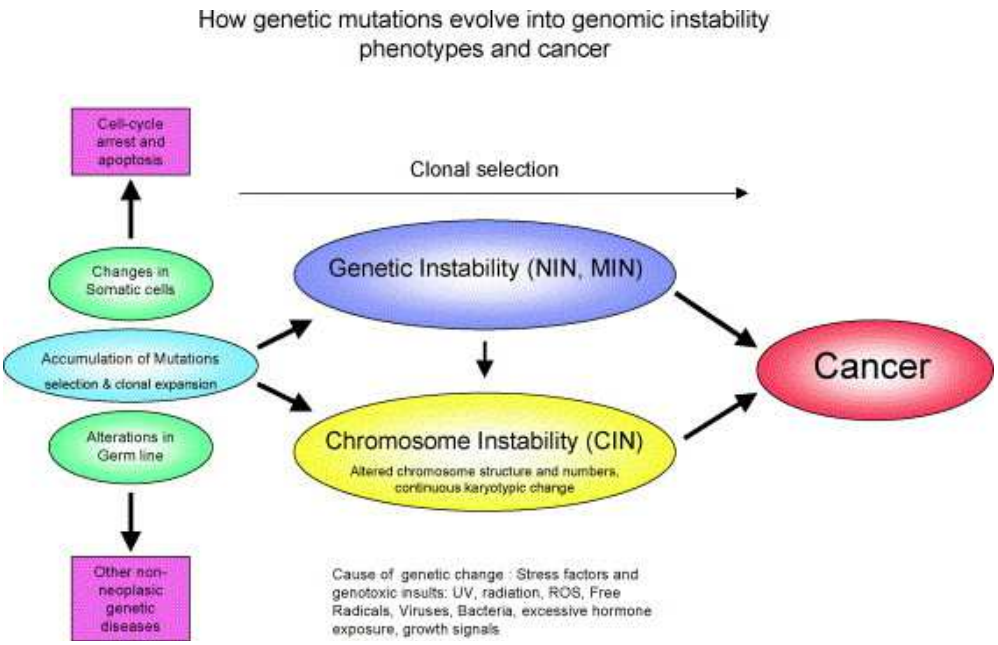

Figure 1: Showing the pathways that link genotoxic stress and genomic instability to cancer (Source: Jefford and Irminger – Finger, 2006)

Chromosomal segregation at cell division is a necessary requirement for genomic stability, therefore any dysregulation in chromosomal segregation or accumulation of chromosome instability results in aneuploidy (Gollin, 2005). As reported by Gollin (2005), abnormal kinetochore – spindle interaction, premature chromatid separation, centromere amplification, multipolar spindles and abnormal cytokines have been associated with aberration in chromosome segregation. Aneuploidy in tumour may have a chromosome numbers ranging from 40 - 60 within a range of diploid cells (Thompson *et al*., 2010). It has also been suggested that chromosomal instability may have dominant traits; this was observed by Lengauer *et al.* (1997).Although normal cells also show chromosomal segregation error at mitosis (Gisselson *et al*., 2010), a negative feedback mechanism appear to be in place that is responsible for the low prevalence rate of aneuploidy in normal cells and suggested that these feedback mechanisms may be lost in malignant cells (Shelter and Amon, 2011).

Mitotic Chromosomal Segregation

Mitosis is a complex process and chromosomes need to be perfectly duplicated and segregate to produce two identical daughter cells (Gardner and Davies, 2009). Chromosome segregation at mitosis is possible through retracting microtubules at sites of merotelic attachments which is then placed at the centromere (Cleveland *et al*., 2003) this ensure that each copy of the chromosome is delivered at each daughter cells. Chromosome loss is associated with loss of centromere integrity and aberrantmerotelic attachments (Jefford and Irminger–Finger, 2006).

Centromere also known as major microtubule organising centre (MTOC) mainly due to their function of nucleate microtubules. In animal cells, the centriole divides into structurally different products one with appendages (mother centriole) and the other without appendages (daughter centriole) and they migrate to opposite poles of the cell (Fukasawa, 2005). In a review by Bornens (2002), it was suggested that the likely reason for these appendages could be for anchoring microtubules.

During anaphase, the centromere divides and the paired chromatids separate establishing cellular shape and polarity therefore during cytokinesis the centromere must duplicate once prior to the next mitosis (Fukasawa, 2005). Abnormality in this process such as abnormal chromosome condensation, defective sister chromatid adhesion and segregation, impaired kinetochore assembly and spindle checkpoint deficiency resulting from karyotype can lead to chromosomal instability (Jefford and Irminger–Finger, 2006).

Chromosomal segregation error at mitosis usually results in aneuploidy, and the subsequent miss - segregated chromosomes are then damaged during formation of new daughter cells. The subsequent DNA double strand breaks in the new daughter cells which usually involves *ATM, CLUK 2* and *p53*, directly result in an unbalanced translocation in the daughter cells (Janssen *et al*., 2011).

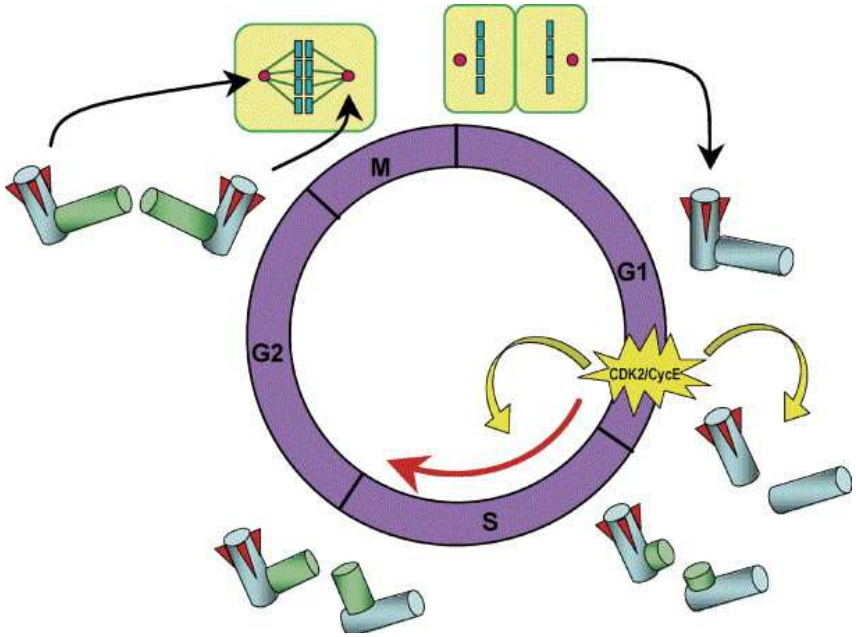

Figure 2: Showing centrosome duplication cycle. Late G1-specific activation of CDK2/cyclin E triggers initiation of both DNA and centrosome duplication. Centrosome duplication begins with the physical separation of the paired centrioles, which is followed by formation of procentrioles near the proximal ends of each pre-existing centriole. During S and G2 phases, procentrioles elongate, and two centrosomes progressively recruit PCM. In late G2, the daughter centriole of the parental pair acquires appendages (shown as red wedges), and two identical centrosomes are generated. During mitosis, two duplicated centrosomes form spindle poles, and direct the formation of bipolar mitotic spindles. Upon cytokinesis, each daughter cell receives one centrosome.
(Source: Fukasawa, 2005).

Cell cycle is tightly controlled bycyclins and cyclin dependent kinase (CDK)(Fukasawa, 2005). The activation of CDK2/ cyclinE triggers centrosome and DNA duplication (Figure 2) under the guidance of *p53,* this process is controlled. Although this normally occur within embryonic cells, CDK2/ cyclinA is responsible for somatic cell centrosome and DNA duplication (Jefford and Irminger–Finger, 2006).

However to avoid *p53* mediated apoptosis, cancer cells may induce supernumerical centrosome clustering in two spindle poles through centromere tension thereby enabling bipolar division, this phenomenon was first observed in mouse neuroblastoma and later in breast cancer (Shao *et al*., 2010). Studies have shown centrosome amplification drives genomic instability (D' Assoro *et al*., 2002), when cells duplicated more than once within a single life cell or failure to undergo cytokinesis due to multiple spindle poles results in genomic doubling as well as increase in centrosome numbers. The paired centriole untimely splits and form individual centrosome, and the resultant formation of centromere without centrioles which function as centrosomes (D'Assoro *et al*., 2002). Overexpression of centrosomal protein (NLP) has been associated with centrosome amplification and reported in breast and lung cancers (Shao *et al*., 2010).

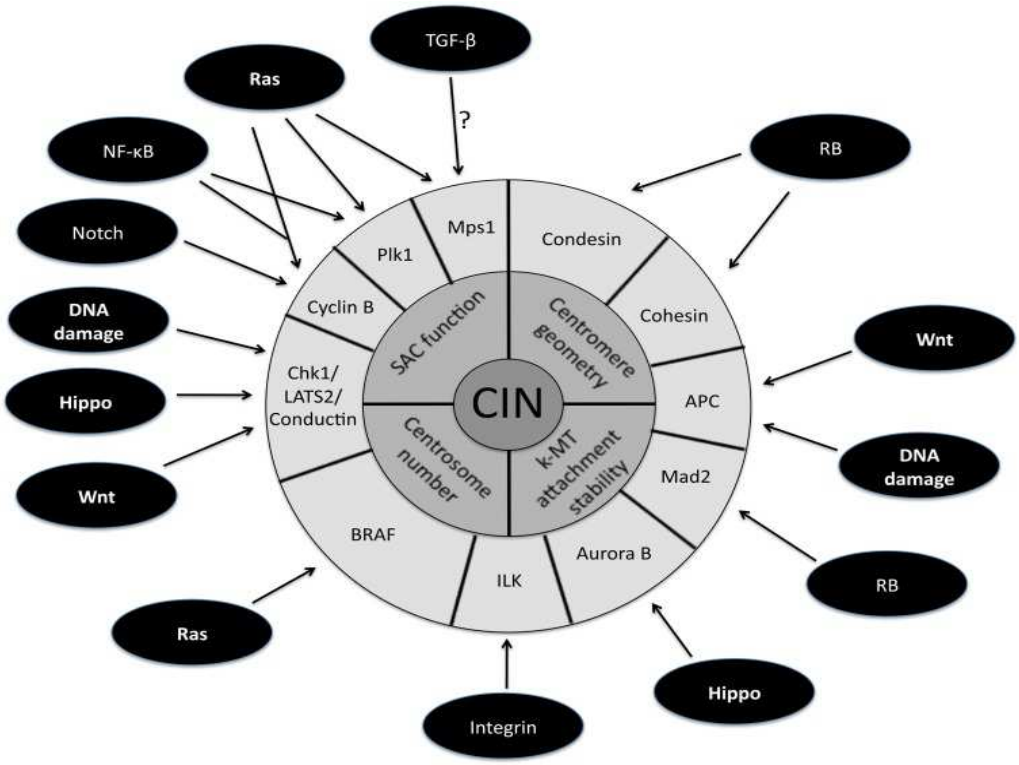

Figure 3: Showing downstream targets of oncogenic signalling pathways that affect mitotic fidelity. (Orr and Compton, 2013)

Whole chromosome gain is the more likely type of chromosomal aberration seen in cancer cells, it has been suggested that deficiency of spindle assembly checkpoint results in a gain of chromosome but the mechanism is still largely unknown (Rajagopalan *et al*., 2004). However spindle assembly deficiency alone is not the cause of continuous generation of trisomies. Other mechanisms suggested by Gisselson *et al*.(2010) include spindle polarity and cytokinesis failure could explain trisomy generation and this has been associated with Wilm's tumour.

A large number of tumours have driver mutation in genes encoding components, figure 3 shows how oncogenes through signalling pathways can also lead to chromosomal instability through mutation of genes encoding proteins involved in mitosis thereby given rise to mitotic infidelity (Orr and Compton, 2013).

Chromosomal misregulation has also been associated with improper k–MT attachment formation, through defect in pericentrometric cohesion and centromere geometry (Orr and Compton, 2013).

Chromosomal Aberration Associated with some cancers

Colorectal cancer

Colorectal cancer has been characterized by numerous chromosomal abnormalities, and the acquisition of genomic instability is a key hallmark to the progression of the tumour (Migliore *et al*., 2011). Chromosomal instability has been associated with 80% - 85% cases of colorectal cancer (Boardman *et al*., 2013; Migliore *et al*., 2011). Others factors reported for genomic instability in colorectal cancer include presences of CpG island methylator phenotype and microsatellite instability (Rajagopalan *et al*., 2003). Shortened telomere has also been linked with chromosomal instability in colorectal cancer (Boardman *et al*., 2013).

Chromosomal rearrangement and numerical abnormalities has been shown to be a common feature in chromosomal instability related colorectal cancer. Migliore *et al.* (2011), observed the "Monosomic type" and reported that loss of chromosome 18, short arm of chromosome 17, 1p, 4, 14, 5q and 21 "monosonic" types evolved toward polyploidy. In contrast, the "trisomic" type observed had gain of chromosome 7, 12, X, 5 and 8 and these were associated with oncogenes. The most frequently observed chromosomal aberration in colorectal cancer are gain of 20q and loss of 18q (Migliore *et al*., 2011). In 2007, Xiao *et al*., observing some Chinese patients reported that the gain of chromosome 20q, 1q, 7q, 17p and 18p, aided colorectal tumour metastasis and suggested that genes responsible for colorectal cancer metastasis might be located in these chromosomes. Recently Hirsh *et al*., (2012) concluded that gain of chromosome arm 20q was an indicator for the progression from adenoma to carcinoma. However, deletion of genes located at chromosome 4 has be associated with the aggressiveness of the tumour (Migliore *et al*., 2011) and Aust *et al*., (2013) recently reported loss of chromosome 4 in colorectal liver metastasis associated with the primary tumour.

Chromosomal structural aberration commonly found in intestinal adenocarcinoma are 8q10 and 17q10; numerical trisomies +7, +13, +20 and +X; monosomies -4, -5, -8, -10, -14, -15, -17, -18, -21, -22 and –Y (Migliore *et al*., 2011). However, progression from adenoma to carcinoma was also associated with loss of 8p21 – pter, 15q11 – q21, 17p12 – 13 and 18q12 – 21 and subsequent gain of 8q23 – qter, 13q14 – 31 and 20q13 (Migliore *et al*., 2011). The unbalanced structure in the chromosome and mutation in genes involved in mitotic checkpoints (*APC*) has also been associated with loss or gain of chromosomal materials and pathogenesis of the cancer (Mularis *et al*., 2008). Structural rearrangement has also been associated with whole chromosome loss and in contrast, chromosomal gain inversely correlates with structural rearrangement (Mularis *et al*., 2008).

Cervical Cancer

Chromosomal abnormality has also been linked with cervical cancer. Human papilloma virus (HPV)has been recognised as the single most important etiological agent for the development of cervical cancer (Munoz, 2000) however, HPV alone cannot cause cervical carcinogenesis (Solima*et al*., 2004). It has been reported that chromosomalloss frequently occurs from chromosomal unstable tetraploidy phenotype leading to the formation of aneuploidy lesions during cervical carcinogenesis (Olaharski *et al*., 2006). The interaction between chromosome 3 and the development and pathogenesis of cervical cancer has been established and disruption of fragile histidine gene, a tumour suppressor gene located in 3p14.2 has been implicated in cervical cancer (Soliman *et al*., 2004; Connolly *et al*., 2000).

It has also been established that the HPV 16 integration site is usually at this fragile locus (FRA3B) that host the *FHIT* and that this integration somehow alter the expression of the gene (Soliman *et al.*, 2004). Furthermore, loss of FHIT protein expression (reduced or absent) have been associated with progression and invasiveness of cervical cancer (Connolly *et al*., 2000). In a meta – analysis by Thomas et al. 2013, the most common chromosomal aberration seen in cervical squamous cell carcinoma was gain of 3q, loss of 3p, loss of 11q, gain of 1q and 5p gain while gain of 17q was more likely to be found in adenocarcinoma suggesting that altered genes located in these regions may provide selection advantage during tumour development.

The relationship between viral HPV oncoprotein (E6 and E7) and loss of function of p53, p21 and pRb, which are key genes responsible for cell cycle and DNA synthesis (Zwerschke and Jansen–Durr, 2000) may result in tetraploidy and possible chromosomal instability leading to aneuploidy (Figure 3). In addition Duensing and Munger in 2002, associated the expression of HPV – 16 E7 and E6 with DNA damage and they suggested that the expression triggered anaphase bridge formation which preceded chromosomal break and alteration in chromosomal structure. They later concluded that expression of HPV – 16 E7 and E6 were a source of numerical and structural chromosome abnormality. However, no convincing evidence suggesting that HPV infection may be responsible for underlying chromosomal instability, that can then create a cellular environment where tetraploidy can proliferate (Olaharski *et al*., 2006). Figure 4 below shows a gain of 3p present in dysplastic precursors (cervical cancer), and this chromosomal aberration defines if the tumour progresses or not, therefore suggesting that a gain of chromosomal material aid cervical cancer development (Reid *et al.*, 2012). Other chromosomal aberration linked with patient prognosis include gain of 3q26, 5p15, 20q13 (Reid *et al*., 2012).

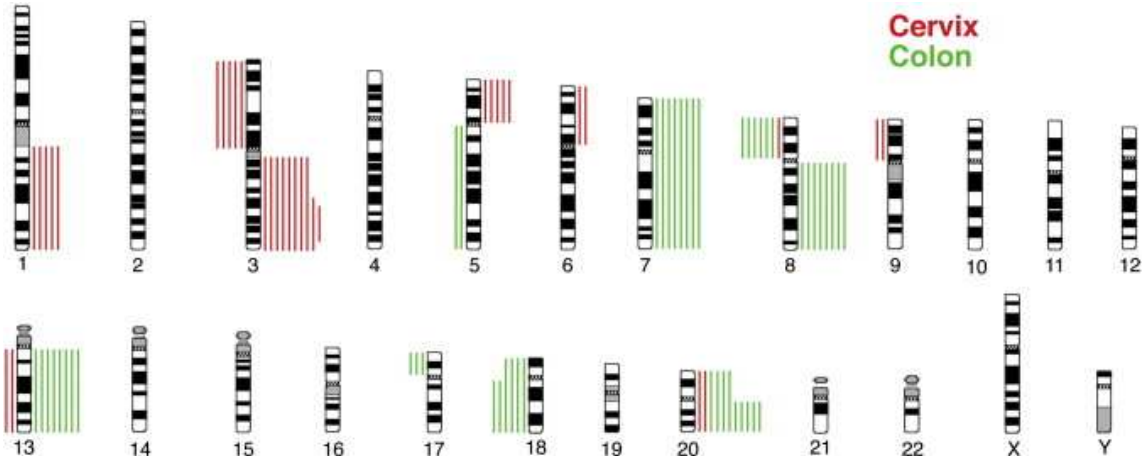

Figure 4: Showing the distribution of chromosomal gains and losses in cervical and colorectal carcinomas. The distribution of genomic imbalances is tumour specific. The results are normalized to n = 10. Note that essentially all cervical carcinomas carry a gain of chromosome arm 3q, and colorectal carcinomas are defined by a recurrent gain of chromosomes 7, 8q, 13, and 20q, and losses of chromosomes 8p, 17p, and 18.
(Source: Reid et al., 2012)

Breast Cancer

Breast cancer is a heterogeneous group of disease and one of the most common malignancies in women (Vasconcelos *et al.,* 2013). Breast cancer has been linked with 3 genomic events; gain or loss of whole chromosome arm and the most frequently seen chromosomal aberration in breast cancer is polysomy of chromosome 17, gain of 1q, gain of 16p and loss of 16q (Kwei *et al*., 2010; Botti *et al*., 2000). DNA amplification particularly 8p12 (*FGFR1*), 8q24 (*MYC*), 11q13 (*CCND1*) and 17q12 (*ERBB2*) (presumptive oncogenic drivers) has also been associated with breast cancer and possible cause of genomic aberration (Kwei *et al*., 2010).

Chromosome 1 and 17 has been thought to be important in the breast cancer carcinogenesis, probably due to fact that genes present at these chromosomes are needed for breast cancer development and chromosomal aberration in chromosome 1 and 7 occur in early in breast cancer tumorigenesis, suggesting that they are involved in the conversion from in situ carcinoma to invasive carcinoma (Botti *et al*., 2000). Monosomy of chromosome 17 seems to be more widely spread than polysomy in non-invasive and low grade in situ carcinoma (Botti *et al*., 2000). In contrast, polysomy of chromosome 17 has also been reported in more invasive type of breast carcinoma suggesting hyperplasia may be relevant in breast cancer tumorigenesis (Reinholz *et al*., 2009). Furthermore, polysomy of chromosome 20 in patients showed poor prognosis of breast cancer when compared to those who had monosomy or disomy (Nakopoulou *et al*., 2002). Kim *et al*. (2012) also reported that chromosome 17 centromere multiplication have also been associated with human epidermal growth factor receptor 2 (HER2) positive breast cancer and patients with this aberration show invasive breast cancer. Reinholz *et al.* (2009), reported that 93% of breast cancer cancers cases had abnormality in chromosome 17 and they further suggested that the reason for this abnormality could be the role of this chromosome in helping the breast cancer in evading apoptosis, unchecked proliferation, invasiveness and possibly promoting angiogenesis.

Muthuswami and colleague recently suggested that the involvement of *EGFR*, *RAS*, *p13k/AKT*, *MYC* and *E2F* signalling in the regulation of some immunoglobulin selected genes that may also aid breast cancer tumorigenesis. It has been reported that in about half of all human cancers, the tumour suppressor gene located on 17p13.1 is either loss or mutated and this aberration has been reported in breast cancer and patients with these abnormalities usually have poor prognosis (Vasconcelos *et al*., 2013).

CONCLUSION

Chromosomal instability does not occur spontaneously, abnormality in cell cycle regulation by key genes (*p53, p21*) and abnormal mitotic chromosomal segregation have been identified as the main cause of aneuploidyand possible tumorigenesis. It has been concluded that abnormality in cell signal pathways can act as a common source of chromosomal instability which will ultimately lead to aneuploidy formation. This loss or gain of chromosomal material could aid the tumour in metastasis, invasiveness or possible resistance to therapeutics. It thus appear that gain of chromosomal material seem to be vital for tumour progression and metastasis. Although, in colorectal cancer a deletion in a key chromosome could also be vital in cancer tumorigenesis. Deletion of chromosome 17 has been reported in most human tumours and it represent a poor prognosis for the disease outcome. However, a gain in chromosome 17 has also been associated with breast cancer tumorigenesis. It has been reported that loss or mutation in *APC*can give rise to polysomy, and this may trigger chromosomal instability and this may define the very start of adenoma to carcinoma sequence.

Numerous studies showing evidence and counter evidence linking loss or gain of chromosomal material to tumour metastasis and poor patient's prognosis of the disease outcome. A loss of a chromosomal material or a structural chromosome aberration could be seen as favourable for one tumour and in contrast represent a poor prognosis for another. The presence of aneuploidy within normal cells are not well tolerated, however aneuploidy in a tumour cell are better tolerated and studies has shown that aneuploidy tolerance by tumour cell may precede the development of cancer tumorigenesis suggesting that this could a ploy by tumour cell to invade or form resistance to therapy.

REFERENCES

Aust, N., Schule, S., Altendorf – Hofman A. K., Chen, Y., Dirsch, O. and Settmacher, U. (2013) Loss of chromosome 4 correlates with better long – term survival and lower relapse rate after RO – resection of colorectal liver metastasis. *Journal of Cancer Research and Clinical Oncology*,**139**(11): 1861 – 1867.

Beckman, R. A. and Loeb, L. A. (2005) Genetic instability in cancer: Theory and experiment. *Seminars in Cancer Biology*,**15**(6): 423 – 435.

Boardman, L. A., Johnson, R. A., Viker, K. B., Hafner, K. A., Jenkins, R. B. and Riegert – Johnson, D. L.(2013) Correlation of chromosomal instability, telomere length and telomere maintenance in microsatellite stable rectal cancer: a molecular subclass of rectal cancer. *PLos One*,**8**(11): e80015.

Bornens, M. (2002) Centrosome composition and microtubule anchoring mechanisms. *Current Opinion in Cell Biology*, **14**: 25 – 34.

Botti, C., Pescatore, B., Mottolese, M., Sciarretta, F., Greco, C. and Di – Filippo, F. (2000) Incidence of chromosome 1 and 17 aneusomy in breast cancer and adjacent tissues: An interphase cytogenetic study. *Journal of American College of Surgeons*, **190**(5):530 – 539.

Cardoso, J., Boer, J., Morreau, H. and Foddle, C. (2007) Expression and genomic profiling of colorectal cancer. *BBA – Reviews on Cancer*, **1775**(1): 103 – 137.

Cleverland, D. W., Mao, Y. and Sullivan, K. F. (2003) Centromeres and Kinetochores: From epigenetics to mitotic checkpoint signalling. *Cell,***112**: 407 – 421.

Connolly, D. C., Greenspan, D. L., Wu, R., Ren, X., Dunn, R. L., Shah, K. V., Jones, R. W. and Bosch, F. X.(2000) Loss of Fhit expression in invasive cervical carcinomas and intraepithelial lesions associated with invasive disease. *Clinical Cancer Research*, **6**(9): 3505 – 3510.

D' Assoro, A. B., Lingle, W. L., and Salisbury, J. L. (2002) Centrosome amplification and the development of cancer. *Oncogene*, **21**(40):6146 – 6153.

Djos, A., Fransson, S., Kogner, P. and Martinsson, T. (2013) Aneuploidy in neuroblastoma tumour is not associated with inactivating point mutations in the STAG 2 gene. *BMC Medical Genetics*. **14**: 102.

Duensing, S. and Munger, K. (2002). The human papilloma virus type 16 E6 and E7 oncoproteins independently induce numerical and structural chromosome instability. *Cancer Research*,**62**:7075 – 7082.

Fukasawa, K. (2005) Centrosome amplification, chromosome instability and cancer development. *Cancer Letters*, **230**(1):6 – 19.

Gardner, A. and Davies, T. (2009) Human genetics. 2nd edition. Oxfordshire, UK. Scion publishing Ltd. Pp. 204 – 381.

Gisselson, D., Jin, Y., Lindgren, D., Persson, J., Gisselsson, L. and Hanks, S. (2010) Generation of trisomes in cancer cells by multipolar mitosis and incomplete cytokinesis. *PNAS*, **107**(47):20489 – 20493.

Gollin, S. M. (2005) Mechanism leading to chromosomal instability. *Seminar in Cancer Biology*,**15**(1): 33 – 42.

Hirsh, D., Camps, J., Varma, S., Kemmerling, R., Stapleton, M., Reid, T. and Gaiser, T. (2012) A new whole genome amplification method for studying clonal evolution patterns in malignant colorectal polyps. *Genes Chromosomes Cancer*,**51**(5): 490 – 500.

Janssen, A., van der Burg, M., Szuhai, K., Kops, G. J. and Medema, R. H. (2011) Chromosome segregation error as a cause of DNA damage and structural chromosome aberration. *Science*, **33**(6051):1895 – 1898.

Jefford, C. E. and Irminger – Finger, I. (2006) Mechanism of chromosome instability in cancers. *Critical Reviews in Oncology/Haematology*,**59**(1):1 – 14.

Kim, A., Shin, H. C., Bae, Y. K., Kim, M. K., Kang, S. H., Lee, S. J. and Lee, E. H. (2012) Multiple of chromosome 17 centromere is associated with prognosis in patients with invasive breast cancers exhibiting normal HER2 and TOP 2A status. *Journal of Breast Cancer*, **15**(1):24 – 33.

Kwei, K., Kung, Y., Salari, K., Holcomb, I. N. and Pollack, J. R. (2010) Genomic instability in breast cancer: Pathogenesis and clinical implications. *Molecular Oncology,***4**(3):255 – 266.

Lengauer, C., Kinzler, K. W. and Vogelstein, B. (1997) Genetic instability in colorectal cancer. *Nature*, **386**:623 – 627.

Luhn, P., Houldsworth, J., Cahill, L., Schiffman, M., Castle, P. E. and Zuna, R. E. (2013) Chromosomal gain measured in cytology samples from women with abnormal cervical cancer screening result. *Gynaecologic Oncology*, **130**(3):595 – 600.

Migliore, L., Migheli, F. and Coppede, F. (2011) Genetics, Cytogenetics and epigenetics of colorectal cancer. *Journal of Biomedicine and Biotechnology*. Available from doi:10.1155/2011/79-2362

Muleris, M., Chalastanis, A., Meyer, N., Lae, M., Dutrillaux, B. and Sastre – Garau X. (2008) Chromosomal instability in near – diploid colorectal cancer: a link between numbers and structure. *PLos One*,**3**(2): e1632.

Munoz, N. (2000) Human papilloma virus and cancer: the epidemiological evidence. *Journal of Clinical virology*,**19**(2):1 – 5.

Muthuswami, M., Ramesh, V., Banerjee, S., Thangaraj, S. V. and Periasamy, J., Rao, D. B. (2013) Breast cancer tumours with elevated expression of 1q candidate gene confer poor clinical outcome and sensitivity to Ras/p13K inhibition. *Plos One*,**8**(10):345 – 349.

Nakopoulou, L., Tsirmpa, I., Giannopoulou, I., Trafalis, D., Katsarou, S. and Davaris, P. (2002) Aneuploidy of chromosome 20 in invasive breast cancer correlates with poor outcome. *Cancer Genetics and Cytogenetics*, **134**(2):127 – 132.

Olaharski, A. J., Sotello, R., Solorza – Luna, G., Gonsebatt, M. E., Guzman, P., Alejandro, M. and Eastmond, D. A. (2006) Tetraploidy and chromosomal instability are early events during cervical carcinogenesis. *Carcinogenesis*,**27**(2):337 – 343.

Orr, B. and Compton, D. A. (2013) A double – edge sword: how oncogenes and tumour suppressor genes can contribute to chromosomal instability. *Frontiers in Oncology*,**3**(164): 12 – 23.

Rajagopalan, H., Jallepalli, P. V., Rago, C., Velculescu, V. E., Kinzler, K. W., Vogelstein, B. and Lengauer, C. (2004) Inactivation of hCDC4 can cause chromosomal instability. *Nature*,**428**(6979):77 – 81.

Rajagopalan, H., Nowak, M. A., Vogelstein, B. and Lengauer, C. (2003). The significance of unstable chromosome in colorectal cancer. *Nature Reviews*, **3**(9): 695 – 701.

Reid, T., Hu, Y., Difilippantonio, M. J., Ghadimi, B. M., Grade, M. and Camps, J. (2012) The consequences of chromosomal aneuploidy on the transcriptome of cancer cells. *BBA – Gene Regulatory Mechanisms*, **1819**(7):784 – 793.

Reinholz, M. M., Bruzet, A. K., Visscher, D. W., Lingle, W. L., Schroeder, M. J., Perez, E. A. and Jenkins, R. B. (2009) Breast cancer and aneusomy 17: Implication of carcinogenesis and therapeutic response. *The Lancet Oncology*, **10**(3):267 – 277.

Sheltzer, J. M. and Amon, A. (2011) The Aneuploidy paradox: cost and benefits of an incorrect karyotype. *Trends in Genetics*, **27**(11):446 – 453.

Shao, S., Liu, R., Wang, Y., Song, Y., Zuo, L. and Xue, L.(2010) Centrosomal NLP is an oncogenic protein that is gene – amplified in human tumours and causes spontaneous tumorigenesis in transgenic mice. *Journal of Clinical Investigation*, **120**(2):498 – 507.

Soliman, P. T., Slomovit, Z. and Wolf, J. K. (2004) Disease mechanisms: Mechanism of cervical cancer. *Drug Discovery Today*, **1**(2):253 – 258.

Thomas, L. K., Bermego, J. L., Vinokurova, S., Jensen, K., Bierkens, M., and Steenbergen, R. (2013) Chromosomal gains and losses in human papilloma virus associated neoplasia of the lower genital tract – A systemic review and meta – analysis. *European Journal of Cancer*. Available from http://dx.doi.org/10.1016/j.ejca.2013.08.022

Thompson, S. L., Bakhoum, S. F. and Compton, D. A. (2010) Mechanisms of chromosomal instability. *Current Biology*, **20**(6):285 – 295.

Vasconcelos, D. S., da–Silva, F. P. E., Quintana, L. G., Anselmo, N. P., Othman, M. A. K., Liehr, T. and de–Oliveira, E. H. C. (2013) Numerical aberration of chromosome 17 and TP53 in brain metastasis derived from breast cancer. *Genetic and Molecular Research*, **12**(3): 2594 – 2600.

Valind, A., Jin, Y. and Gisselsson, D. (2013) Elevated tolerance of aneuploidy in cancer cells: Estimating the fitness effects of chromosome number alterations by in silico modelling of somatic genome evolution. *PLos One*, **8**(7):e70445

Xiao, X. Y., Zhou, X. Y., Yan, G., Sun, M. H. and Du, X. (2007) Chromosomal alteration in Chinese sporadic colorectal carcinoma detected by comparative genomic hybridization. *Diagnostic Molecular Pathology*, **16**(2):96 – 103.

Zwerschke, W and Jansen–Durr, P. (2000) Cell transformation by the E7 oncoprotein of human papilloma virus type 16: interaction with nuclear and cytoplasmic target protein. *Advanced Cancer Research*, **78**: 1 – 29.