



Imbalance is not an impediment: understanding the natural imbalances of Sex and B-chromosomes in species by understanding cancer karyotypes

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Cancers are defined by abnormal karyotypes, displaying ever-changing structural and numerical abnormalities. Such plasticity of the karyotype underlies the evolution of cancer cells (Navin et al. 2011, Pavelka, Rancati, and Li 2010, Lee et al. 2011, Nicholson and Duesberg 2009). Karyotype alterations are also responsible for phenotypic variation and evolution in yeast (Rancati et al. 2008, Pavelka, Rancati, and Li 2010) and arguably of species in general (King 1993, McCarthy 2008). Because the alterations in the karyotypes of cancer cells have been shown to be non-random and stable within limits (Li et al. 2009, Nicholson and Duesberg 2009, Gebhart and Liehr 2000, Mertens et al. 1997), recently it has been proposed that carcinogenesis may be a form of speciation (Duesberg et al. 2011, Vincent 2010)

Typical species karyotypes, however, are largely composed of balanced karyotypes. While chromosomal balance *appears* to be the standard, there exist two classes of chromosomes that display a natural existing imbalance, namely, sex chromosomes and B-chromosomes. To understand the behavior of these “normal” aneuploidies I compare and contrast their behavior to aneuploid chromosomes in cancer.

SEX CHROMOSOMES AND B-CHROMOSOMES

Sex chromosomes display different ratios per species per sex determination system (i.e. XY in mammals and XO in flies). Such chromosomal imbalance is thought to be sustainable because it is balanced by dosage compensation where XX females transcriptionally inactivate one X chromosome and XY or XO males show double the transcriptional activity. Recent work however has called this sweeping conclusion into question (Mank, Hosken, and Wedell 2011). Accordingly, X chromosomes in humans previously thought to be completely inactivated show over 15% of genes without dosage compensation (Carrel and Willard 2005). Moreover, chicken and zebra finch show no sex chromosome dosage compensation (Itoh et al. 2010, Ellegren et al. 2007) nor does silkworm (Zha et al. 2009, Arunkumar, Mita, and Nagaraju 2009). In fact, expression differences in sex chromosomes may actually confer differences in sex determination (Smith et al. 2009).

Another natural chromosomal imbalance is seen in B-chromosomes. The definition of B-chromosomes changes with author and year, however it is sufficient to state that they are unique extra chromosomes.

B-chromosomes, like sex chromosomes, are thought to have originated from autosomes (Keyl and Hagele 1971, Wilkes et al. 1995) or sex chromosomes (Camacho, Sharbel, and Beukeboom 2000).

They are present in numerous different organisms from fungi to mammalia and can range in size and structure from a small fragment to the largest chromosome in the karyotype (Gregory 2005). While B-chromosomes have been identified in various species, their functionality remains largely unknown. It is known that B- chromosomes can change the expression levels of A-chromosomes (Kirk and Jones 1970, Ayonoadu and Rees 1971) and accordingly, induce phenotypic changes such as different sex traits in cichlids (Yoshida et al. 2011) or leaf color in corn (Staub 1987). Certain changes conferred by B-chromosomes, have shown corresponding adaptive effects. *Avena sativa* with B-chromosomes shows resistance to rust (Dherawattana and Sadanaga 1973) and the fungus *Nectria haematococca* with B-chromosomes are resistant to antibiotics (Miao, Covert, and VanEtten 1991, Miao, Matthews, and VanEtten 1991). The observations in sex and B-chromosomes beget the question: is perfect balance necessary?

ARE ANEUPLOID AND/OR MARKER CHROMOSOMES IN CANCER THE SAME AS B-CHROMOSOMES?

The benefits of aneuploidy in cancer, largely thought as a detriment, are slowly being appreciated (Pavelka, Rancati, and Li 2010). Similarly, B-chromosomes which were once thought to “have no useful function at all to the species carrying them.”(Ostergen 1945), appear to persist because of potential advantageous effects. Indeed, the “drive” of B-chromosomes, that is an increase in frequency in species, generally increases over time (Cavallaro et al. 2000, Araújo et al. 2002). Further, listing the behavior between B- chromosomes and aneuploid marker chromosomes in cancer shows a remarkable concordance (Table 1). Such a similarity enforces the idea that carcinogenesis is perhaps a form of speciation and that karyotypic alterations such as B-chromosomes and sex chromosomes are the same as aneuploid marker chromosomes in cancer.

TABLE 1. B-CHROMOSOMES VS. ANEUPLOID/MARKER CHROMOSOMES IN CANCER

| Effect/phenotype | Aneuploidy/ marker chr. | B-chromosome | Citation |
|--|----------------------------|--------------|---|
| Only a minority are maintained in karyotype | Yes | Yes | (Gregory 2005, Li et al. 2009) |
| Degree of stability in mitosis correlated with chromosome size | Yes | Yes | Nicholson, unpublished (Hewitt 1979) |
| Increase in structural change/ recombination | Yes | Yes | (Camacho et al. 2002, Fabarius, Hehlmann, and Duesberg 2003, Janssen et al. 2011) |
| Pleiotropic effect on genome expression | Yes | Yes | (Upender et al. 2004, Ruiz-Rejon, Posse, and Oliver 1980) |
| Slowed growth/development | Yes | Yes | (Torres et al. 2007, Harvey and Hewitt 1979) |
| Confers adaptive potential | Yes | Yes | (Lee et al. 2011, Dherawattana and Sadanaga 1973) |

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