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Intragenomic conflict and cancer

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Summary Intragenomic conflict occurs when some elements within the genome produce effects that enhance their own probability of replication or transmission at the expense of other elements within the same genome. Here it is proposed that mutations involved in intragenomic conflict are particularly likely to be co-opted by evolving lineages of cancer cells, and hence should be associated with the occurrence of cancer. We discuss several types of intragenomic conflict that are associated with various forms of cancer. © 2002 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Cancer has afflicted humanity for millenia (1), and is a major cause of mortality in current human populations (2). Cancer actually constitutes a variety of distinct diseases, specific to a particular tissue type and causal mechanism (3). Nevertheless, there are specific molecular, biochemical and cellular traits shared by all types of cancer (3). Cancer is characterized by one defining feature: it is a disease of uncontrolled cellular growth and replication (4). This problem is not restricted to humans: a variety of non-human animals also succumb to various sorts of cancer (4).

The development of cancer is a multi-stage process involving successive mutational changes within a single cell lineage (5). The process, from the initial mutation to malignancy, may involve up to six or seven separate mutations and take decades for completion. There are two basic types of cancer mutations: enhanced growth and replication and prevention of growth and replication penalties (4). These mutations are usually associated with specific classes of genes, particularly proto-oncogenes and tumor-suppressor genes (*6*).

Proto-oncogenes suffering mutational damage can be transformed into oncogenes, which can accelerate the rate of cell growth and proliferation (7). Over a hundred distinct proto-oncogenes and tumor-suppressor genes have been identified (8). These genes play pivotal roles in regulating the cell division cycle. Proto-oncogenes are highly conserved across distantly related organisms, such as yeast, worms, flies and humans. This suggests that they play key functional roles in very basic aspects of cell physiology. Tumor-suppressor genes implement crucial 'check-point' controls that stop the progression of the cell cycle if something has gone wrong. These genes carry out functions analogous to genome 'policing' (*9*) at the intercellular level. Both proto-oncogenes and tumor-suppressor genes have played critical roles in cellular replication across hundreds of millions of years of evolution (8), and tumor-suppressor genes have recently been shown to carry out policing functions in invertebrates as well as vertebrates (10).

The prevalence of cancer is not surprising if we consider the fact that every cell in every organism is derived from an ancient lineage of germ plasm, which has never, over the course of hundreds of millions of years, stopped dividing and replicating (11). Of course, all of the somatic cells in our bodies are supposed to stop replicating or replicate at a reduced, controlled rate. But the fact that each somatic cell lineage within our bodies is derived from a lineage of cells that has been replicating continuously for hundreds of millions of years emphasizes the inherent problem faced by mechanisms designed to halt or reduce cell growth and replication. An ingenious series of regulatory mechanisms has evolved to prevent the occurrence of uncontrolled growth. A large series of such failsafe mechanisms makes the probability that any

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particular cell will proliferate uncontrollably very small (12). However, the human body consists of literally trillions of cells.

The evolutionary explanation for the success of this kind of regulation is that it allows the evolution of large, multicellular organisms, that are able to successfully propagate their genes by effectively manipulating their environment (13). Multicellularity involves many examples of extreme cellular altruism, in which one cell or group of cells sacrifices themselves for the good of other cells that make up the entire body (particularly the reproductive cells). The reproductive benefits of such altruism are high because each cell is clonally related to each other cell in the body.

However, conflict can arise, even between cells or organisms that are identical by descent (12). A mutation in a cell causing the replication of its own genome, even at the expense of its clonal relatives, will have an advantage, *ceteris paribus* (because other cells will not contain the new mutation). Hence cancer can be seen as the result of a conflict between short-term interests of the cell and long-term interests of the individual. The development of cancer proceeds in a manner formally analogous to Darwinian evolution, in which a succession of changes, each conferring some type of advantage in terms of cellular growth or replication, leads to the progressive conversion of normal cells into cancer cells (5).

There is substantial evidence for the action of natural selection in the development of cancer (4) including: 1. The recurrence of identical mutations associated with cancer (both inherited and de novo); 2. Evidence for positive selection of specific amino acid changes in cancer clones; 3. Comparative analysis of normal and mutated proteins, revealing the mechanism of action of the mutated proteins in promoting cancer development; 4. Experimental addition or deletion of suspect genes (or their mutated forms) via genetic engineering (14).

Nevertheless, the genetic similarity of members of a cellular lineage (i.e., an organism) enhances the potential for lineage selection: selection in favor of strategies that suppress strategies successful on only a short timescale (12). Cancer is the result of proliferating cells (successful on their timescale) jeopardizing a larger population of cells (the individual). Nunney (12) argues that lineage selection will act to decrease the success of cancerous mutants by increasing the number of genes recruited to control cell proliferation.

Hence, cancer can potentially be explained in two different ways: 1. as the result of accidental failures of a series of regulatory mechanisms; or 2. as the result of the evolution of clonal cancer cell lineages via natural selection on recurring selfish (at the cellular level) mutations. These two explanations are not mutually exclusive, and both are likely to be involved in any particular incidence of cancer. However, the genetic conflict generated by cancer is actually a subset of a much larger category of genetic conflicts that are collectively known as intragenomic conflict (15).

The purpose of this article is to argue that intragenomic conflict, because of the nature of the genes involved, is particularly likely to give rise to effects that are likely to be co-opted by evolving lineages of cancer cells, even though intragenomic conflict may rarely involve direct selection for cancerous growth (i.e., growth of one cell lineage at the expense of the rest of the organism).

First, we will briefly introduce the concept of intragenomic conflict, and discuss how alleles evolved in the context of intragenomic conflict could promote the development of cancer. Then we will discuss four specific examples of intragenomic conflict that appear to be associated with an increased probability of cancer: genomic imprinting, sex chromosome drive, cytoplasmic elements and genetic transposition. Finally, we will discuss a few predictions of the hypothesis that intragenomic conflict can facilitate the development of cancer.

INTRAGENOMIC CONFLICT

In general, we expect genes within an organism to produce effects that enhance the survival or reproduction of the whole organism, because such effects benefit all of the genes. This is because most genes are in 'the same boat' with respect to transmission to the next generation. However, there are opportunities for genes to enhance their own future prospects at the expense of other genes in the same genome (16). This creates the conditions for intragenomic conflict, in which different elements within the same genome cause contradictory effects, aimed at either enhanced replication or the repression of such enhancement. Genes that produce effects that enhance their replication at the expense of other elements of the genome are called selfish genetic elements, ultra-selfish genes, or genetic parasites, among other names (17). Intragenomic conflict occurs because there are multiple genetic entities within the genome (e.g., paternal and maternal halves of the nuclear genome, cytoplasmic element genomes, transposable elements, etc.), and these elements do not all have the same mode of inheritance, the same opportunities for self-replication, the same relatedness to genetic elements in other genomes, or the same information about their relatedness to other genetic elements in other genomes (17). Thus, some genes (such as mitochondrial genes) can enhance their own prospects of replication by reducing the number of male offspring produced, or diverting resources to female offspring. However, such tactics are likely to reduce the fertility of the organism as

a whole, which then causes selection to favor the evolution of suppressors in other (unlinked) regions of the genome.

Cancer is an opportunistic disease, and the likelihood of developing cancer is closely associated with the activities of the cells in particular regions and at particular ages within an organism. Children don't typically develop types of cancer that are common in adults. Instead, children tend to get cancers of tissues that are very active in early development (4). This occurs because cells in these developing tissues are required to display traits that are characteristic of cancer cells: rapid growth and replication, invasion of other tissue, and movement among tissue types (4). In a similar manner, genes involved in intragenomic conflict are engaged in activities that are particularly likely to be co-opted by cancer cells for their own nefarious purposes.

Cancer cells often co-opt normal regenerative processes to aid in cancer progression. For example, bone resorption and remodelling processes that release growth factors normally used for repair are usurped by colonizing cancer cells (4). Hahnahan and Weinberg (3) argue that the development of cancer requires the conscription of non-cancerous cells and normal gene products into the process of tumorigenesis, specifically by promoting the release of growth-stimulating signals. Genes involved in intragenomic conflict are predisposed to participate in this kind of effect.

Evolution by natural selection works with the materials at hand. Tools evolved via natural selection for one purpose are often co-opted for other uses (18). There are a variety of examples of this phenomenon in the literature (18). In most cases, when we think of such pre-adaptations, we are thinking of co-option of a feature that serves the organism in one capacity to serve that same organism in another capacity, although there are some interesting cases where an adaptation on the part of a host serves as a pre-adaptation for a manipulation by a parasite (13). However, when multiple levels of selection are involved (e.g., whole organism, cells within the organism, genes within genomes), then the possibility of co-option of an adaptation at one level of selection to serve the purpose of (or respond to selection at) another level is a possibility. For example, selection favors protease production by embryonic trophoblast tissues during pregnancy, which allows the trophoblast to invade the maternal circulation. This kind of invasion is produced by selection on embryos engaged in parent–offspring conflict over resource allocation (19), and also by conflicting selection pressures on different genomes (maternal and paternal) within the embryo (a form of intragenomic conflict; (20)). The powerful biochemical armaments produced by these genes (such as proteases) may be co-opted by selection acting at the level of cellular competition within the individual (i.e., cancer). The switching on of such genes in contexts other than their original one may aid cancerous or pre-cancerous cell lineages in achieving freedom from regulation by the body politic. For example, proteases are an important tool used by cancerous cell lineages in metastasis (3).

GENOMIC IMPRINTING AND GROWTH FACTORS

Genomic imprinting occurs when the expression of a gene is dependent upon which parent the gene derives from (21). Imprinted genes are not expressed: for example, a maternally imprinted gene is not expressed by the maternal half of the genome in an individual. A variety of explanations for genomic imprinting have been proposed (22). David Haig (23) has developed an elegant theory that explains the phenomenon of genomic imprinting as the result of genetic conflict between the maternal and paternal genome within a single embryo.

In organisms in which mothers regulate the supply of nutrients to their offspring over long periods (e.g., pregnancy in mammals), selection may affect the maternal and paternal half of each embryonic genome differently. This is particularly likely in promiscuous species, in which current or consecutive embryos are likely to be unrelated to each other through the paternal lineage (i.e., they are likely to have different fathers). The maternal half of the genome retains a high probability of relatedness to other embryos via the maternal lineage. In this case, the paternal half of the genome is selected to be more 'selfish' (i.e., to attempt to acquire more resources from the mother) than the maternal half of the genome within any single embryo. Hence, Haig hypothesized that genomic imprinting typically represents a struggle for resources between the maternal and paternal halves of the genome, with the maternal half imprinting (silencing) the expression of genes promoting growth (and associated increases in the acquisition of resources from the mother), and the paternal half imprinting the expression of genes that suppress such growth effects (24).

Other explanations of the adaptive significance of genomic imprinting have been proposed (25), but these theories are not logically consistent and have not been supported by more recent evidence (26). Recent efforts aimed at developing Haig's theory of genomic imprinting using sophisticated theoretical models support the validity of the hypothesis (27).

Approximately 30 genes in the genome are known to be imprinted, although researchers believe there are probably many more yet to be identified (21). Many of these genes are involved in fetal growth and development (28), and more are involved in growth than would

be expected by chance (21). One class of genes which has been studied in the context of genomic imprinting is the insulin-like growth factors (IGFs).

IGFs are involved in the regulation of cell proliferation, differentiation, apoptosis, and transformation (29). They exert their actions by interacting with specific receptors on the cell membrane, and the interaction is regulated by a group of specific binding proteins. IGFs are important promoters of cell growth and proliferation, as their name suggests (29). IGFs can also act as cell survival signals, acting to prevent apoptosis (30).

One of the best know cases of genomic imprinting involves IGF-2 (31,32). In mice, IGF-2 is maternally imprinted (32), and so the maternal copy is not expressed. IGF-2 binds to two different receptors in mammals. The first type (type 1) mediates most of the growth promoting effects of IGF-2 (33). The type 2 receptor, which is encoded by a gene called IGF-2r, is apparently derived from a mannose 6-phosphate receptor (34). The main function of mannose 6-phosphate receptors is the transportation of molecules to lysosomes for degradation (35). The IGF-2 type 2 receptor is paternally imprinted, so that it is exclusively expressed by the maternal genome (36). Apparently, the IGF-2r functions to degrade IGF-2 (37). Hence, there is a biochemical tug of war between IGF-2 (promoting growth) and IGF-2r (restricting growth by degrading IGF-2) in mice (23). IGF-2 and IGF-2r are also imprinted in humans, although paternal imprinting of IGF-2r is not absolute (38).

Diseases of enhanced growth, such as acromegaly, are associated with increased risk of cancer (39–41). Research has demonstrated that high circulating levels of growth factors, such as insulin-like growth factors, are associated with increase for a variety of common cancers, such as those of the breast (42), prostate (43), lung (44), and colon (45). These studies are typically prospective, so that cancer occurred long after the levels of IGF were determined. Hence, cancer is unlikely to have caused the elevated IGF levels detected in high-risk individuals in these studies.

Recent research makes it clear that there is a connection between genomic imprinting, growth factors (e.g., IGFs) and cancer (46). A number of studies have now found connection between loss of imprinting and cancer. For example, loss of imprinting of the IGF-2 gene is seen in a variety of cancers: Wilms' tumor (47); renal cancer (48); colon cancer (49); prostate cancer (50); ovarian cancer (51); and breast cancer (52), among others. Children in whom maternal imprinting of IGF-2 fails (and hence have two active copies of IGF-2), are predisposed to Wilms' tumor (53). Beckwith–Wiedemann syndrome, a fetal overgrowth syndrome that produces a pre-disposition to cancer, is associated with loss of imprinting of IGF-2, as well as other genes (54).

Under Haig's hypothesis, the very evolution of the genomic imprinting system itself is a result of genetic conflict between maternal and paternal halves of the genome within the embryo, over the course of evolutionary history. The maternal and paternal halves of the genome in live-bearing vertebrates are engaged in a cross-generational biochemical tug of war, with the paternal half of the genome producing chemical signals that promote cell growth and proliferation of the embryo, and the maternal half expressing genes that reduce cell growth and proliferation (e.g., decoy receptors). If this hypothesis is correct, then it makes sense that the loss of imprinting in genes that are normally maternally imprinted would enhance the probability of cancer, because such genes tend to promote cell growth and replication, and because they are expressed at high levels (because they are typically counteracted by suppressors). Increasing the dosage of such genes should be expected to have tumor-promoting effects. Like any complex system, there are a variety of ways in which the imprinting system can malfunction. Because imprinted genes are frequently involved in cell growth and replication, malfunctions of the imprinting system are particularly likely to give rise to cancer.

Cancer may also result from the malfunction of paternally imprinted genes. Under-expression of growth-controlling factors (via mutational loss of function in the maternal copy of a gene that is paternally imprinted) would enhance the probability of tumor development. TSSC3, a paternally imprinted human gene on chromosome 11 that is homologous to a mouse gene that regulates apoptosis (55), is a likely candidate for this kind of effect, as is the transforming growth factor beta type II receptor (56).

SELFISH SEX CHROMOSOMES

Hurst (57) has presented the argument that the non-recombining part of the Y chromosome (the NPAR region) should act as a magnet for genes with growth-promoting effects. The logic of this argument is similar to that described above for genomic imprinting. When females typically have more than a single mate, then the Y chromosome in a given fetus will not necessarily be related to Y chromosomes in other embryos. Hence, selection should favor Y chromosomes that promote the growth of their own body at the expense of their 'siblings'.

A variety of evidence indicates that genes on the Y chromosome have growth-enhancing effects in mammals (57). Traditionally, the Y chromosome has been considered to be genetic 'desert', with few active genes,

but recent research (58) has overturned this view, providing evidence that a number of genes crucial to growth and development occur on the Y chromosome (59). The presence of extra Y chromosomes is associated with high growth rates and large size (60). Burgoyne (61) demonstrated that genes on the Y chromosome cause rapid growth of XY embryos relative to XX embryos prior to implantation in mice. This effect has also been found in other species (rats, cows and humans), and has been found to continue after implantation (62). Studies on tooth crown size and structure of individuals with various sex chromosome anomalies indicate that the Y chromosome codes for growth factors that lead to sexual dimorphism in tooth size and shape (63). The Y chromosome is thought to have at least one gene region that influences stature in humans, called Growth Control Y (64,65). This region is likely to be different than the region controlling differential growth of XY and XX embryos (66). Recent analysis has identified specific regions of the Y chromosome associated with specific growth factors (65,67).

The growth-promoting effects of genes on the Y chromosome should make them likely to promote cancer. The presence of extra Y chromosomes is associated with some forms of cancer (68). For example, expression of the Zfy gene is associated with prostate cancer (69). Differential expression of several other Y chromosome genes has been found in prostate cancer progression (70,71). Over-expression of MIC2 gene is linked to the occurrence of Ewing's sarcoma (72). Pronounced expression of the Amg gene is found in ameloblastoma tumors (73).

Some forms of cancer have been found to be associated with genetic variation of X-linked genes (e.g., (74,75)). This makes sense in light of Hurst's (57) view of the X and Y chromosome as involved in a biochemical tug of war, in which there is a 'stalemate', with each party producing factors that counter the factors produced by the opponent. Evidence suggests that the X chromosome may suppress growth when associated with a Y chromosome, but not when associated with another X chromosome (76). Genes on the X chromosome may also produce 'conditional' growth factors, which enhance growth when present in a female (XX) embryo, but not when in a male (XY) embryo (77). This would have the effect of counteracting the selfish tendencies of the Y chromosome, resulting in a more equitable distribution of resources among embryos (77). Over-expression of these X-linked growth factors would have the same tendency to produce cancer as over-expression of Y-linked growth factors.

Hurst (77) argues that conflict between the X and Y chromosomes may explain the evolution of X chromosome growth factor genes that escape X-inactivation (and thereby increase the growth of XX embryos relative to XY embryos). Such genes would also be expected to increase predisposition to cancer. Recent evidence suggests that a number of X-linked genes escape X-inactivation, and there is considerable interest in the role of such genes in the development of cancer (78). Hurst (77) discusses evidence that many of the genes that escape X-inactivation are growth factors, as predicted by genetic conflict theory.

Hurst (77) also hypothesizes that the X and Y chromosomes in mammals are engaged in an evolutionary 'arms race', in which both Y-linked growth factors and X-linked growth suppressors increase in copy number over evolutionary time. Increase in the copy number of Y-linked growth factors provides the potential for a dramatic increase in gene dosage in the absence of suppression (i.e., when the X-linked suppressor is deleted or non-functional). Tandem repeats are subject to relatively high probabilities of gain or loss due to errors during crossing-over in meiosis (79). These two factors (increased dosage and high probability of gain or loss due to crossover errors) may interact to increase the degree to which Y-linked growth factor genes enhance the probability of cancer.

CYTOPLASMIC ELEMENTS

Cytoplasmic elements are genetic elements that exist in the cytoplasm and are inherited from parent to offspring. These elements often have a different mode of inheritance from nuclear genes, which brings them into conflict with the nuclear genome (17). There is also conflict between different cytoplasmic elements (of the same or different strains) for representation in the cytoplasmic 'commons' (80). This type of competition leads to strong selection in favor of high replication rate (81). This, in turn, can lead to a higher mutation rate as proofreading mechanisms are sacrificed or abbreviated in the interests of faster replication rates. Recent research suggests that mtDNA heteroplasmy occurs with substantial frequency (82).

Mitochondria are well-known cytoplasmic elements that have many of the properties described above. Mitochondria are hypothesized to have evolved from an endosymbiont, and they replicate by binary fission independently of the eucaryotic cell cycle (83). Mitochondrial DNA has uniparental inheritance via the maternal lineage. Research suggests that mitochondrial genomes have been under strong selection for high replication rates (84). Mitochondrial DNA is also known to have high substitution rates compared to nuclear DNA (85), and this is believed to be due to a lack of some of the proofreading mechanisms found in nuclear DNA (86). Mutations of mitochondrial DNA are associated

with a wide variety of diseases (87). Mitochondrial mutations are commonly associated with cancer (88). Some mitochondrial mutants associated with disease have been shown to have particularly high replication rates which allow them to outcompete normal mitochondria in intracellular selection experiments (89).

The mitochondrion is a product of two genomes that must function in concert. The signals that most likely control mitochondrial biogenesis are poorly understood, although nuclear transcription factors that appear to regulate mitochondrial genes have been found (90).

In the past few years it has been determined that mitochondria are central to the process of apoptosis in many types of cells (91,92). Mitochondria release factors that are part of the pathway of apoptosis. Apoptosis, or programmed cell death, is the mechanism whereby mutated or diseased cells are eliminated. Apoptosis is specifically blocked in cancer cells (3). The function of the tumor suppressor p53, which is mutated in over 50% of cancers, is to assess the cells for damage and trigger apoptosis if the damage is beyond repair.

It appears that the mitochondrion and mitochondrial function are key components of apoptosis and proliferation in colon cancer cells (93). Mitochondrial transcription is down-regulated, cell growth is increased, and apoptosis is blocked in these cells; triggering of apoptosis is associated with an increase in mitochondrial function. Thus, in these cells, normal mitochondrial function is necessary for apoptosis and is inhibited in cancer cells. Thus, the mitochondrion, an entity with a high potential for intragenomic conflict, is a major regulatory point for cancer.

Several mitochondrial genes that have been implicated in cancer may be involved in intragenomic conflict. For example, the mitochondrial elongation factor Tu, necessary for protein synthesis in mitochondria, has been found to be over-expressed in tumor cells (94). The Bcl-2 proto-oncogene was originally discovered as a chromosomal translocation leading to the up-regulation of the gene in B cell lymphoma (95). It has since been determined that Bcl-2 is over-expressed in different types of cancer cells, including lymphoma, breast and prostate (96–98). The Bcl-2 protein serves as a prototype for a whole family of proteins localized to mitochondria that are either pro- or anti-apoptotic (99,100). Bcl-2 is found in the outer mitochondrial membrane and blocks apoptosis in part by blocking the release from mitochondria of cytochrome c, a factor that triggers subsequent steps in the apoptotic pathway (92). It is not known what other functions, if any, Bcl-2 has, but some hypothesize that it is involved in mitochondrial association with the cytoskeleton through microtubular contact (101).

Therefore, there appears to be a link between genes involved in mitochondrial function and biogenesis and cancer. It will be interesting to determine if other genes that have the potential for intragenomic conflict may be found to be associated with mitochondrial biogenesis.

TRANSPOSABLE GENETIC ELEMENTS

It is well known that certain kinds of viral infections are associated with the development of cancer (102,103). For example, the hepatitis B virus accounts for the majority of liver cancer cases worldwide(104). It is also well-established that certain types of retroviruses cause cancer by acquiring proto-oncogenes from the host genome (105). When these genes are reinserted into the host genome (via reverse transcription) they have been converted into oncogenes (106). Often these oncogenes encode growth factors that promote cell growth and proliferation (107). Overexpression of these viral oncogenes is caused by various mechanisms, including the addition of enhancers and promoters, and by gene amplification (e.g., (108)). Viral oncogenes can also interfere with the regulatory mechanisms that normally control cell growth (109). This can lead to rapid cell proliferation and associated cancer. From an evolutionary perspective, the tendency of certain retroviruses to incorporate and exploit proto-oncogenes makes senses as a device to enhance the population size of the virus within the body of the host, and there is evidence that cancer progression is associated with viral replication (110).

Retroviruses are widespread and abundant components of vertebrate genomes (111). Retroviruses are similar to other kinds of transposable elements that are not horizontally transmitted between hosts (112). These transposable elements can make up large portions of the genome (113). They apparently exist as parasites of the functional part of the genome, that is, the part that carries out the tasks involved in constructing and maintaining a functional organism (114). Tranposition by transposable elements is often harmful to the host organism (115). Transposable element insertions are known to be a major cause of spontaneous mutation in natural populations of *Drosophila* (116). It is likely that a balance between selection for representation within the genome (intragenomic selection) and selection among genomes (organismal selection) determines the amount of such parasitic DNA within the genome (117). It is not clear whether retroviruses evolved from transposons, or vice versa, and both kinds of evolutionary transitions may be common (118).

The fact that transposable elements are extremely common, and are capable of disrupting the genome as a result of transposition, suggest that these elements may frequently promote cancer (119). Transposable elements

could promote cancer by disrupting the function of regulatory genes (e.g., tumor suppressor genes). Transposable elements may also promote cancer in a manner similar to retroviruses, by utilizing proto-oncogenes to promote their own replication, converting those genes to oncogenes in the process. Human LINE-1 retrotransposons are linked to a variety of different forms of cancer (e.g., (120)). Other transposable elements have been implicated in cancer as well (121).

In conclusion, by their very nature, genes involved in intragenomic conflict are likely to be disruptive and to promote uncontrolled growth and replication. Such genes are inherently likely to be exploited by cancer cell lineages as they evolve toward escape from control by the body. Future work should focus on localizing other genes involved in intragenomic conflict, to determine if they are associated with particular types of cancer.

PREDICTIONS

A variety of predictions can be derived from the hypothesis that intragenomic conflict and cancer will often be associated. Here we provide a few basic predictions:

1. Loss of imprinting mutations in (normally) maternally imprinted genes should be associated with an increased risk of cancer, whereas loss of imprinting mutations in paternally imprinted genes should not. Conversely, malfunctions of the maternal copy of paternally imprinted genes should be associated with an increased risk of cancer.
2. Species with high levels of promiscuity should be more prone to the development of cancer than monogamous species, *ceteris paribus*.
3. Species in which the sex chromosomes make up a larger portion of the genome should be more prone to cancer.

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