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Imprinting of a Genomic Domain of 11p15 and Loss of Imprinting in Cancer: An Introduction[1]

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Abstract

Our laboratory has found genomic imprinting of a large genomic domain of human 11p15.5, identifying six imprinted genes within this domain: (*a*) insulin-like growth factor II (IGF-II), an important autocrine growth factor in a wide variety of malignancies; (*b*) *H19*, an untranslated RNA that is a putative growth suppressor gene regulating IGF-II; (*c*) $p57^{KIP2}$, a cyclin-dependent kinase inhibitor that causes G_1-S arrest; (*d*) K_VLQT1, a voltage-gated potassium channel; (*e*) *TSSC3*, a gene that is homologous to mouse *TDAG51*, which is implicated in Fas-mediated apoptosis; and (*f*) *TSSC5*, a putative transmembrane protein-encoding gene. We hypothesize that 11p15 harbors a large domain of imprinted growth-regulatory genes that are important in cancer. Several lines of evidence support this hypothesis: (*a*) we have discovered a novel genetic alteration in cancer, loss of imprinting, which affects several of these genes, and is one of the most common genetic changes in human cancer; (*b*) we have found that the hereditary disorder Beckwith-Wiedemann syndrome, which predisposes to cancer and causes prenatal overgrowth, involves alterations in $p57^{KIP2}$, *IGF-II*, *H19*, and K_VLQT1; (*c*) we have found both genetic (somatic mutation in Wilms' tumor) and epigenetic alterations (DNA methylation) in cancer; and (*d*) we can partially reverse abnormal imprinting using an inhibitor of DNA methylation. We propose a model of genomic imprinting as a dynamic developmental process involving a chromosomal domain. According to this model, cancer involves both genetic and epigenetic mechanisms affecting this imprinted domain and the genes within it.

Introduction

I appreciate the opportunity to present a brief introduction to the relationship between genomic imprinting and cancer. This review is not meant to be comprehensive but is rather meant to serve only as an introduction to our own laboratory's approach to this problem, and I refer readers to a more comprehensive review of the subject published elsewhere (1).

Genomic imprinting is defined as an epigenetic modification of a gene or the chromosome on which it resides that is present in the gamete or zygote and leads to differential expression of the two parental alleles of the gene in somatic cells of the offspring. Typically, imprinting results in monoallelic expression, so for some genes, it is the paternal allele that is expressed, and for others, it is the maternal allele. However, imprinting does not always involve exclusive monoallelic expression. Of course, imprinting is reprogrammed during development because a paternal gene in one generation could be a maternal gene in the next.

Imprinting challenges two assumptions of conventional human Mendelian genetics: that the two alleles of a gene are equivalent and that there is no pathology associated with two functioning copies of a gene. In fact, geneticists tend to believe that if a patient has only one functioning copy of a gene, then the patient either has a dominantly transmitted disorder or is a carrier for a recessive trait. As will be discussed below, LOI[3] in cancer involves a failure of the cell to maintain normal monoallelic expression of some imprinted genes.

Imprinting has been thought to be involved in cancer for over 20 years, from the study of two types of rare tumors. A complete ovarian teratoma, a benign tumor, arises from parthenogenesis; *i.e.*, there are 46 chromosomes, but they are all derived from the mother (2). The converse is a malignant hydatidiform mole, which is androgenetic (3). The lesson of these two tumors is that a normal pregnancy requires 46 chromosomes, but the chromosomes must be from both mother and father. An imbalance of parental input may lead to a neoplasm, and the type of tumor depends on whether the parental genetic excess is maternal or paternal.

Genomic imprinting in cancer entered a semimolecular era ~10 years ago, when it was discovered that a number of chromosomal alterations in cancer, including LOH and gene amplification, show preferential involvement of one specific parental chromosome (4–6). One implication of preferential parental involvement in LOH is that an imprinted gene is lost and the expressed allele is on the parental chromosome. As will be discussed later, abnormal imprinting in cancer can also involve activation of a normally silent allele of a gene. However, proof of either hypothesis required the identification of specific imprinted genes and elucidation of their role in cancer.

BWS and Genomic Imprinting

Our laboratory's interest in genomic imprinting began with a patient who presented to our institution's clinical service with an ear crease, large tongue, and omphalocele. Abdominal ultrasound examination revealed hepatomegaly, nephromegaly, and Wilms' tumor, which was cured operatively. The patient, of course, had BWS, but he was unusual in that he was the proband of a large multigenerational BWS kindred, allowing us to perform linkage analysis and map the gene to 11p15.5 (7).

In collaboration with Marcel Mannens and Jan Hoovers of the University of Amsterdam, we focused our efforts on fine-mapping BWS patients with rare balanced germ-line chromosomal rearrangements, using fluorescent *in situ* hybridization with yeast artificial chromosomes and, ultimately, cosmids derived from them. Our initial hypothesis was that a single BWS gene would span these breakpoints. This effort led to the identification of two clusters of BWS germ-line chromosomal rearrangement breakpoints, termed BWSCR1 and BWSCR2. Six breakpoints lay within BWSCR1, over a distance of 350 kb, which also included a balanced chromosomal translocation that was the sole cytogenetic abnormality in a rhabdoid tumor, and we focused our subsequent cloning efforts on this region (8).

Early in the analysis of these chromosomal rearrangement patients, it became apparent that all of the balanced rearrangements were of maternal origin (8, 9). In addition, a second type of chromosomal rearrangement in BWS involves unbalanced duplications of 11, and these are always of paternal origin (9). Thus, this molecular cytogenetic analysis suggested a role for imprinted genes on chromosome 11 in the pathogenesis of BWS. However, precise delineation of such a

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[3] The abbreviations used are: LOI, loss of imprinting; LOH, loss of heterozygosity; BWS, Beckwith-Wiedemann syndrome; STF, subchromosomal transferable fragment; IGF-II, insulin-like growth factor II.

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role awaited the identification of specific imprinted genes on this chromosome. Imprinting of 11p15 genes was also suggested by the observation of Junien and colleagues (10) of paternal uniparental disomy in some BWS patients.

Independently of these experiments, we and others had mapped a region of LOH in embryonal and adult tumors to 11p15 (reviewed in Ref. 11). To localize more precisely the region harboring a putative tumor suppressor gene, we transferred STFs of 2–5 Mb from 11p15 and identified a region that suppressed *in vitro* the growth of the rhabdomyosarcoma cell line RD (12). This region overlapped BWSCR1, and we, therefore, focused our subsequent efforts on this region.

Identification of Imprinted Genes on 11p15 and Loss of Imprinting in Cancer

Because chromosomal alterations in BWS and LOH in embryonal tumors show preferential involvement of a specific parental allele, we looked for evidence of imprinting of genes that mapped within or near BWSCR1. At the time, no human genes had been shown at the molecular level to be imprinted, although the gene for IGF-II and *H19*, the human homologues of which mapped just telomeric to BWSCR1, were known to be imprinted in the mouse (13, 14). IGF-II is an important autocrine growth factor in a wide variety of malignancies (15, 16), and *H19* is an untranslated RNA that is a putative growth suppressor gene (17).

The paradigm for these experiments was IGF-II. Two different polymorphisms, an *Apa*I site and a dinucleotide repeat length polymorphism, can be used to distinguish maternal and paternal alleles in heterozygotes. After reverse transcription-PCR on normal cellular RNA, only the paternal allele was seen, indicating that the gene is expressed monoallelically from the paternal allele (18). To distinguish between genomic imprinting and simple allelic exclusion, the paternal allele must be found to be expressed exclusively in separate individuals. Similarly, H19 showed preferential expression from the maternal allele, and both genes were thus expressed with the same pattern of imprinting in the mouse (18).

When we examined Wilms' tumors, we were surprised to find that, in 70% of cases, both alleles of IGF-II were expressed. The term that we coined for this genetic alteration was LOI, which simply means loss of parental origin specific expression, and it can represent either abnormal activation of the normally silent allele or abnormal silencing of the normally expressed allele of a given imprinted gene (1, 18, 19). LOI was not limited to tumors because we and others observed biallelic expression of IGF-II in the normal tissue of patients with BWS as well (19, 20). This is an important observation mechanistically because it means that LOI is not just an epiphenomenon of the tumor: it can arise in normal tissues of patients.

We also observed silencing of the maternal allele of *H19* in Wilms' tumors that showed biallelic expression of IGF-II, suggesting that a domain of genes on the maternal chromosome may undergo LOI (19). In those cases, LOI is the functional epigenetic equivalent of the genetic alteration caused by uniparental disomy. However, not all tumors show LOI involving multiple genes within the domain. For example, we and others found that H19 is not silenced in hepatoblastomas with LOI of IGF-II (21, 22). Nevertheless, we have observed that LOI can also involve silencing of maternally expressed imprinted genes at some distance from IGF-II but still within the normally imprinted domain, as discussed below.

LOI has become a focus of many laboratories, and it is one of the most common genetic alterations in cancer, albeit an epigenetic one, involving all of the embryonal tumors of childhood as well as lung, ovarian, renal, gastric, breast, and hepatocellular cancer (reviewed in Ref. 1). Recently, we have also observed LOI in chronic myelogenous leukemia, but here it appears to have a different role. The stable phase of chronic myelogenous leukemia is a relatively benign disease caused by the bcr-abl translocation. Patients do not become significantly ill until they enter accelerated phase and blast crisis, for which there is no specific molecular marker. LOI was associated specifically with disease progression but not with stable phase (23). This observation could have considerable clinical significance, in that decisions regarding the timing of bone marrow transplantation could benefit from the use of a biological marker that precedes progression to the accelerated phase and blast crisis.

In work published after the General Motors conference, we also identified LOI in both cancer and normal tissue of a subset of patients with colorectal cancer. Approximately 40% of colorectal cancer patients showed LOI in their cancers and matched normal mucosa, compared to only 13% of the colons of patients without cancer, suggesting that LOI may identify or even predispose to colon cancer in some patients (24). Consistent with this idea, tumors with LOI were particularly common among those with microsatellite instability, suggesting a potential link between abnormal imprinting in cancer and abnormal DNA replication or repair (24).

A Cluster of Growth-related Imprinted Genes on 11p15

Given the coincident location of BWSCR1 and the tumor-suppressing STF described earlier, we embarked on an effort to identify additional genes on 11p15 as candidate imprinted and/or tumor suppressor genes. Using the STF as a starting point, we derived a P1 artificial chromosome and cosmid contig across a 2-Mb region from D11S12 to tyrosine hydroxylase, performed exon trapping from this genomic DNA, and identified 15 genes within this region. The imprinted genes within this group are clustered and described below.

***IGF-II* and *H19*.** *IGF-II* and *H19* were first identified as candidate imprinted genes, as described above.

***p57^{KIP2}*.** *p57^{KIP2}* is a cyclin-dependent kinase inhibitor that causes G_1-S arrest and corresponds to a conserved sequence within the cosmid contig, for which a cDNA clone that is of the same family as p27 and p21 had been identified by Steve Elledge's laboratory. We found that *p57^{KIP2}* contains a transcribed repeat encoding proline-alanine, so we termed it the PAPA repeat. Using this polymorphism, we found that $p57^{KIP2}$ is imprinted and expressed from the maternal allele (25). We and others have observed mutations in $p57^{KIP2}$ in ~5% of BWS patients but not in Wilms' or other tumors (26, 27). In addition, some Wilms' tumors show LOI of $p57^{KIP2}$ (25, 28). In the case of $p57^{KIP2}$, unlike that of IGF-II, LOI involves silencing of the normally expressed maternal allele (28). A $p57^{KIP2}$ deletion mutant is lethal in mouse when maternally transmitted, and the embryos show omphalocele and adrenocytomegaly (29). However, these mice do not show other features of BWS, and paternal transmission exhibits no phenotype (29). Nevertheless, paternally inherited mutations in $p57^{KIP2}$ do give rise to a mild BWS phenotype, indicating that the gene must not be fully imprinted in some tissues in at least some stage of normal human development, and that haploinsufficiency of $p57^{KIP2}$ is responsible for at least some of the clinical stigmata of BWS (26).

***K_VLQT1*.** *K_VLQT1* is a very large gene that we identified from exon trapping, corresponding to a longer isoform of the known *K_VLQT1* gene and encoding a voltage-gated potassium channel; mutations of this gene cause the cardiac conduction disorder long QT syndrome. Amazingly, all of the BWSCR1 chromosomal breakpoints fell within this gene, although long QT syndrome does not show any of the characteristics of an imprinted gene, such as parent of origin effect (30). The explanation for this paradox was the observation that alternative splicing of the gene leads to several isoforms, one of which

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is specific to the heart and is not imprinted prenatally or postnatally and another of which is expressed ubiquitously and is imprinted prenatally (30).

TSSC3. *TSSC3* is the third novel gene we isolated from a tumor-suppressing STF, a 2-Mb multigene region that suppresses the growth of rhabdomyosarcoma (RD) cells *in vitro*, hence the name TSSC3 (for *t*umor-*s*uppressing *S*TF *c*DNA *3*). *TSSC3* is homologous to mouse *TDAG51*, which induces fas and fasL, causing apoptosis of T lymphocytes in mice (31). The gene is potentially interesting for two reasons. First, it is imprinted and expressed from the maternal allele, and it has a potential growth-inhibitory function, like other maternally expressed imprinted genes in this region (32). Second, it is only 14 kb telomeric to *hNAP2* (31), another gene we identified that is not imprinted (33), which is a homologue of a gene that promotes nucleosome assembly in yeast. Thus, *TSSC3* and *hNAP2* define a potential centromeric boundary region between imprinted and nonimprinted 11p15 genes. Our laboratory is actively testing this region for functional activity using heterologous systems.

TSSC5. This gene encodes a putative transmembrane protein, based on its predicted sequence (34). It is expressed at high levels in fetal liver and kidney, suggesting a potential role in embryonal tumors. *TSSC5* is imprinted and expressed from the maternal allele. We have also found mutations of this gene in some patients with Wilms' tumor (34). Thus, *TSSC5* could be inactivated in Wilms' tumor by mutation, maternal LOH, or both. However, the gene is not imprinted in adult tissue, and we have found somatic mutations and LOH of the remaining normal allele of *TSSC5* in lung cancer (34). Thus, *TSSC5* may act as an imprinted tumor suppressor gene in embryonal tumors, with LOH as the primary means of inactivation, but as a conventional Knudsonian two-hit tumor suppressor gene in adult tumors.

Other Genes. Another imprinted gene in this region is the maternally expressed *ASCL2* (35), the human homologue of the mouse *Mash2* gene, but it is not a focus of our laboratory or this review. Subsequent to this lecture, we identified two novel nonimprinted genes that flank *TAPA1* (CD81), and that we termed *TSSC4* and *TSSC6*, suggesting that the 11p15 imprinted domain includes separately regulated imprinted subdomains (42). In addition, several laboratories including our own have identified potentially imprinted expressed sequence tags within the K_VLQT1 gene, the functional significance of which has not yet been established.

Discussion

In summary, 11p15 harbors an ~1-Mb domain of growth-related imprinted genes (Fig. 1). Several of these genes show genetic and/or epigenetic alterations in cancer or cancer-predisposing syndromes, including *IGF-II*, *H19*, $p57^{KIP2}$, K_VLQT1, and *TSSC5* (Fig. 1). One or multiple genes can be affected in a given patient, suggesting that these genes are independently important in cancer but can also be regulated as a domain of imprinted genes. Although animal models suggest a potential direct role of IGF-II imprinting in carcinogenesis (36), the other imprinted growth-related genes we have identified within this domain also are likely to be important.

DNA methylation is also consistent with the domain hypothesis. Alterations in DNA methylation were first identified in cancer over 15 years ago (37). DNA methylation is important in both normal imprinting in development (38) and abnormal imprinting in cancer (19). We have found that we can restore normal imprinting from abnormally imprinted tumor cells using 5-aza-2′-deoxycytidine, a drug that inhibits DNA methylation (39). This reversal of LOI appears to affect multiple genes within the imprinted domain, consistent with a genomic domain model of imprinting affecting multiple genes (37).

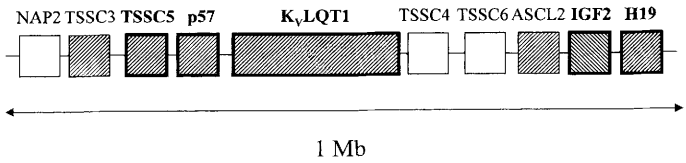

Fig. 1. A genomic domain of growth-related imprinted genes on 11p15.5. The figure depicts the relative position of a large (1-Mb) genomic domain of imprinted genes isolated from 11p15.5 (not drawn to scale). ▧, paternally expressed genes; ▨, maternally expressed genes; □, nonimprinted genes. Genes that have shown genetic alterations in cancer or BWS at the DNA level, or epigenetic alterations at the level of imprinting, are shown in *boldface type*.

These experiments also suggest a potential novel therapeutic strategy for cancer targeted at epigenetic mutations.

We have previously proposed a model of normal imprinting that is also consistent with the data on pathological imprinting summarized here (40). According to this model, imprinting does not involve a simple single gametic mark. Although there certainly is such a mark early in development, other factors also play a role in propagation of an imprint during development, including tissue-specific *trans*-acting factors and local *cis*-acting changes, such as alterations in DNA methylation. According to this model, alterations in imprinted genes in cancer could involve several different types of alterations in the control of normally imprinted genes. These changes could include: separation in the germ line of an imprinted gene from an imprinting control center; alterations in a *cis*-acting but distant regulatory sequence controlling the entire domain; alterations of locally *cis*-acting regulatory sequences, such as DNA methylation; changes in or near the sequence of a gene itself that renders it nonimprintable; or loss of development and tissue-specific *trans*-acting modifiers that maintain normal imprinting in cells. I believe that, over time, we will find a number of molecular causes for LOI in cancer, just as we have found several mechanisms for conventional mutational alterations in tumor-related genes.

An intriguing new lead into one possible mechanism of LOI comes from experiments on the mouse K_VLQT1 gene (41). We found that K_VLQT1 imprinting was relaxed during development, as in the human. However, the degree of relaxation of imprinting was strain background dependent (41). To our knowledge, this is the first example of strain-dependent developmental relaxation of imprinting of an endogenous gene. The implication is that LOI in human cancer could involve abnormality of mechanisms similar to those involved in normal relaxation of imprinting in development. We are now performing back-cross experiments in mice to try to identify potential modifier genes that might influence both normal genomic imprinting and abnormal imprinting in cancer.

Finally, I wish to cite all of the past and present members of the laboratory who have performed the work briefly summarized here. In particular, Shirley Rainier first observed LOI in cancer; Linda Kalikin mapped the BWSCR1 breakpoints; Ren-Ju Hu performed exon trapping and identified several novel genes; Maxwell Lee identified normal and abnormal imprinting of K_VLQT1, *TSSC3*, and *TSSC5*; Hengmi Cui found LOI in colon cancer; Shan Jiang performed the mouse experiments; and Glenn Miller (Genzyme Corp.) collaborated on DNA sequencing.

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