Jumping Translocation Breakpoint Regions Lead to Amplification of Rearranged Myc

To the Editor:

The amplification of cellular proto-oncogenes, a common feature of malignant tumors, results in distinct cytogenetic alterations in carcinomas and hematopoietic neoplasms. In carcinomas, it mainly produces elongation of chromosomes by homogeneously staining regions or extrachromosomal elements referred to as double minutes. In hematopoietic malignancies, in which homogeneously staining regions and double minutes are rare, it gives rise to jumping translocations of chromosomal segments containing oncogenes, i.e., segmental jumping translocations (SJT). SJTs were detected recently in treatment-related leukemias in humans.1 They have been shown to relocate chromosomal segments containing oncogenes, i.e., segmental jumping double minutes are rare, it gives rise to jumping translocations of poietic malignancies, in which homogeneously staining regions and elongation of chromosomes by homogeneously staining regions or malignant tumors, results in distinct cytogenetic alterations in carcinoma.

To the Editor:

Flow sorting.5 The genomic DNA obtained from flow-sorted chromosomes contained the same clonotypic MOPC 315-typical T(12;15) translocation breakpoint region. This region is known to harbor a recombined and transcriptionally deregulated Myc gene.

Spectral karyotyping (SKY)2,3 was used to analyze the chromosome complement of a subline of the inflammation-induced mouse plasmacytoma, MOPC 315. It readily identified the Chr T(12;15), the hallmark chromosome of BALB/c plasmacytoma, MOPC 315, in which it effected the transposition onto two marker chromosomes of a chromosomal segment that contained the same clonotypic MOPC 315-typical T(12;15) translocation breakpoint region. This region is known to harbor a recombined and transcriptionally deregulated Myc gene.

The amplification of cellular proto-oncogenes, a common feature of malignant tumors, results in distinct cytogenetic alterations in carcinomas and hematopoietic neoplasms. In carcinomas, it mainly produces elongation of chromosomes by homogeneously staining regions or extrachromosomal elements referred to as double minutes. In hematopoietic malignancies, in which homogeneously staining regions and double minutes are rare, it gives rise to jumping translocations of chromosomal segments containing oncogenes, i.e., segmental jumping translocations (SJT). SJTs were detected recently in treatment-related leukemias in humans.1 They have been shown to relocate chromosomal segments containing oncogenes, i.e., segmental jumping double minutes are rare, it gives rise to jumping translocations of poietic malignancies, in which homogeneously staining regions and elongation of chromosomes by homogeneously staining regions or malignant tumors, results in distinct cytogenetic alterations in carcinoma.

The mechanism of the SJT that amplified the T(12;15) breakpoint region in MOPC 315 is not known. Possibilities include, first, the involvement of extrachromosomal precursors, such as episomes or double minutes containing T(12;15) translocation segments, before a postulated chromosomal reintegration event; second, the occurrence of illegitimate, nonreciprocal, trans-chromosomal recombinations between hyperreplicative or fragile sites; and third, the involvement of recombinogenic repetitive sequences at the breaksites. The latter explanation is supported by findings that breakpoints of jumping translocations, the next close relatives of SJT, are usually found at sites of repetitive DNA, eg, in centromeres or pericentromeric heterochromatia,4 telomeres, subtelomeric regions, variant telomeric repeats or interstitial telomeric sequences,5-11 or constitutive heterochromatin12,13; however, this has not been shown for MOPC 315. Furthermore, it is conceivable that the Myc gene facilitates its own amplification via SJTs as a consequence of a Myc-induced mutator phenotype. This hypothesis is based on the proposal that Myc acts as a mutator gene in plasmacytomases14 and the finding that chromosomal translocations were induced by another oncogene, the SV40 large T-antigen.15

In conclusion, it is suggested that SJTs may be not only a mechanism for increasing the copy number of unrearranged oncogenes, but also a tumor progression mechanism that leads to the amplification of rearranged, transcriptionally active oncogenes. Additional studies are warranted to determine the prevalence of SJTs in mouse plasmacytomases and to explore if recombined oncogenes can jump in human leukemias and lymphomas, too.

ACKNOWLEDGMENTS

The authors thank Dr J.F. Mushinski for reading the letter and making helpful editorial suggestions.

Allen E. Coleman
Alexander L. Kovalchuk
Siegfried Janz
Division of Basic Sciences
National Cancer Institute
Bethesda, MD
Alessio Palini
FAST Systems
Gaithersburg, MD
Thomass Ried
Genome Technology Branch
National Center for Human Genome Research
National Institutes of Health
Bethesda, MD

REFERENCES

Fig 1. Amplification of T(12;15) translocation breakpoint regions by segmental jumping translocation (SJT) in BALB/c mouse plasmacytoma, MOPC 315. (A) SKY display image of MOPC 315. Rearrangements between Chr 12 and 15 (indicated by arrows) were observed consistently in 30 images on both the plasmacytoma-specific chromosome T(12;15) and the marker chromosomes, T(12;15;16;12;15;16) and T(17;15;16;12;15;16). The chromosomes are numbered I, II, and III, respectively. (B) Reverse painting of flow-sorted tumor chromosomes on normal mouse chromosomes stained with DAPI. The normal DAPI-stained chromosomes are shown in the white insets to facilitate the interpretation of the reverse painting results. Three distinct flow peaks designated I, II, and III were identified (not shown). They must have contained the translocated chromosomes I, II, and III (shown in [A]) for the following reasons. Peak “I” contained Chr T(12;15) because the translocation juxtaposed the Ig heavy-chain gene cluster, located on Chr 12F2, to the Myc locus, residing on Chr 15D2. Therefore, upon reverse painting, Chr 12 should be labeled completely in red (with the exception of the small telomeric cap distal to band F2 that is not discernible in the image due to its small size), whereas Chr 15 should be labeled from band D2 to the telomere. The observed reverse-painting pattern depicted at the top matched this expectation. Peak “II” contained Chr T(12;15;16;12;15;16), because the FISH probe derived from it stained the distal half of Chr 16, but not Chr 17. Peak “III” contained Chr T(17;15;16;12;15;16), because the FISH probe obtained from it stained both Chr 16 and Chr 17. Thus, the reverse painting pattern of the three flow peaks corresponded to the structure of the translocated chromosomes as predicted by SKY. (C) Detection of the same clonotypic junction fragment between the switch region (Sα) of the Ig heavy chain α gene (Cα) and intron 1 of Myc by direct, two-round PCR amplification with nested primer pairs (arrowheads). The identical hybrid fragment (indicated by the two-colored horizontal bar) was obtained when DNA samples prepared from the flow-sorted marker chromosomes I, II, and III were used as templates in three different PCR reactions. DNA sequence analysis confirmed the identity of the Myc/Sα breaksite and its flanking regions on all three chromosomes. Twenty basepairs of Myc and Sα are shown at the bottom to left and right of the breakpoint, respectively. Exons 2 and 3 of Myc, exon 1 of Cα, and Sα are depicted as labeled boxes. The T(12;15) translocation breaksite is indicated by an arrow.

**Relationship Between Levels of Leptin and Hemoglobin in Japanese Men**

To the Editor:

Leptin, the ob gene product secreted by adipocytes, decreases food intake while it increases energy expenditure and functions as an important signal for the regulation of body weight. Leptin acted synergistically to increase erythroid development in vitro. Hematopoiesis is thought to be regulated by erythropoietin, which, in adults, is produced mainly in kidneys, in response to hypoxia. Leptin production occurs mainly in adipocytes, but there has been no report showing that adipocytes have a sensor for hypoxia. It is interesting that bone marrow contains many adipocytes, the role of which is not clear.

Although the effect of leptin on hematopoiesis may be modest, the results of our epidemiologic study, together with those of previous studies performed in vitro, suggest that leptin may play some role in hematopoiesis in humans. Further cross-sectional and prospective studies are needed to elucidate the role of leptin in hematopoiesis.

---

**Table 1. Relationship Between Levels of Leptin and Hemoglobin in Male Workers**

<table>
<thead>
<tr>
<th>Hemoglobin (g/dL)</th>
<th>&lt;14.5</th>
<th>14.5-15.8</th>
<th>≥14.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>148</td>
<td>422</td>
<td>138</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.7 (0.5)</td>
<td>45.9 (0.3)*</td>
<td>44.6 (0.6)†</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>22.30 (0.2)</td>
<td>23.2 (0.1)†</td>
<td>24.1 (0.2)‡</td>
</tr>
<tr>
<td>Exercise (times/mon)</td>
<td>2.8 (0.3)</td>
<td>2.5 (0.1)</td>
<td>1.8 (0.2)*</td>
</tr>
<tr>
<td>Cigarettes (pieces/d)</td>
<td>13.0 (1.3)</td>
<td>12.6 (0.7)</td>
<td>14.9 (1.4)</td>
</tr>
<tr>
<td>Alcohol (mL/wk)</td>
<td>202.0 (15.0)</td>
<td>197.0 (8.3)</td>
<td>203.0 (15.6)</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>3.37 (0.14)</td>
<td>3.61 (0.09)</td>
<td>3.68 (1.58)</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>3.90 (0.17)</td>
<td>4.56 (2.24)†</td>
<td>5.40 (0.31)†</td>
</tr>
</tbody>
</table>

Values are mean (SE). *P values are versus the group with hemoglobin levels of <14.5 g/dL. Lean analysis was performed using the general linear regression model procedures of Statistical Analysis System (SAS Institute, Cary, NC).

*P < .01.
†P < .001.
‡P < .05.
Jumping Translocation Breakpoint Regions Lead to Amplification of Rearranged *Myc*

Allen E. Coleman, Alexander L. Kovalchuk, Siegfried Janz, Alessio Palini and Thomas Ried