Identification of the Constant Chromosome Regions Involved in Human Hematologic Malignant Disease

Abstract. Specific consistent chromosome translocations are regularly observed in certain human leukemias and lymphomas. For the majority of leukemias, the constant recombinants are: the long arm of 9 to chromosome 22 in chronic myeloid leukemia, the long arm of 21 to chromosome 8 in acute myeloblastic leukemia, and the long arm of 17 to chromosome 15 in acute promyelocytic leukemia. Three related translocations are seen in Burkitt lymphoma and B cell acute lymphocytic leukemia; in each one, chromosome 8 is involved with chromosome 21, 14, or 22. Analysis of a complex translocation affecting chromosomes 8 and 14 indicates that the translocation of chromosome 8 to chromosome 14 is the critical constant rearrangement. The analysis of the DNA at the translocation sites of these chromosomes, rather than the reciprocal of each translocation, appears to be the most productive focus for initial study. In experimental approach, it would be useful to distinguish which of the two rearranged chromosomes that result from a reciprocal translocation merits initial detailed analysis. In the myeloid leukemias, the two translocation chromosomes are each involved only with the other in most instances, and there appears to be no reason a priori to choose one recombinant chromosome over the other. Fortunately, each of the three common translocations, 9;22 (1), 8;21 (16), and 15;17 (17), also occurs in a variant form in a limited number of patients, and these can be used to determine whether one recombinant chromosome is constant the variant forms (Fig. 2). For the translocations in AML and APL, one recombinant chromosome is constant and one is variable (the constant one is enclosed in a box in Fig. 2). For CML, the situation is more complex; this may merely reflect the fact that we have data on more than 100 CML patients whose cells were studied with banding, as compared to only about 100 AML patients with 8;21 translocations and 50 to 60 APL patients with a 15;17 translocation. The standard 9;22 translocation occurs in about 92 percent of

Several consistent translocations that are relatively specifically associated with particular types of human leukemia and lymphoma have been identified during the past 8 years (1). These include the translocations between chromosomes 9 and 22 in chronic myeloid leukemia (CML) (2), between chromosomes 8 and 21 in acute myeloblastic leukemia (AML-M2) (3), and between chromosomes 15 and 17 in acute promyelocytic leukemia (AML-M3) (4). Three variant translocations, each involving chromosome 8, have been observed in Burkitt lymphoma and acute lymphocytic leukemia (ALL) of B cell origin, which may be two clinical manifestations of the same malignant disease. The three translocations include the one originally identified by Zech et al. (5) involving chromosomes 8 and 14 (5, 6) as well as two recently described variants, one between 8 and 2 (7) and the other between 8 and 22 (8). The breakpoint in No. 8 appears to be in the same band in the long arm (8q24) (Fig. 1) in all three translocations. These various translocations appear to be reciprocal; DNA measurements show that there is no gross loss of chromosomal DNA in the 9;22 translocation in CML (9).

Interest in defining the DNA sequences at the sites of these translocations has been further stimulated by the recent finding that the three immuno-
Fig. 2. (A) Diagrammatic representation of the break points and the chromosome exchange in the simple consistent translocations in CML, AML, and APL. (B) Schematic drawing of the break points and the typical pattern of chromosome exchange observed in the complex variants affecting each of these translocations. The other chromosome involved in these complex rearrangements varies. For each type of leukemia, the rearranged chromosome that is constant in both the simple and complex translocations is enclosed in a box.

more than general notions. However, the observations of Neel et al. (21) suggest an examination of the function of consistent chromosome rearrangements. Their studies have shown that, in chickens, tumors induced by the avian leukemia virus have viral integration sites in common, and that these sites are expressed at high levels (21). They suggest that there has been proviral integration adjacent to a specific cellular gene, with the viral promotor enhancing the expression of this gene.

These concepts can be applied to the consistent translocations summarized in this report to yield the following model. For the translocations seen in lymphoid tumors, it is proposed that the gene adjacent to the Ig locus or the Ig locus itself is related to control of cell proliferation. The gene on 8q would act as a promotor; this gene might be one of the long terminal repeats or pseudogenes that are scattered throughout the genome. As a result of the translocation, this promotor would be moved next to the Ig genes, causing expression of the latter, with subsequent cell proliferation and transformation. It is equally possible that theactivation occurs in the other direction, that is, that the promotor of the Ig gene is active in B cells when placed next to certain sequences on chromosome 8, would activate a locus on No. 8 whose function might be to stimulate lymphoid cell division with subsequent transformation. Unfortunately, the gene loci in myeloid cells that are analogous to the Ig loci in lymphoid cells have not yet been distinguished. It is thus possible that an active promotor is the step that is currently under investigation, highly probable that the DNA sequences at the sites of specific translocations will be identified before their function is defined.

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References and Notes


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Suppression of Reflex Postural Tonus: A Role of Peripheral Inhibition in Insects

Abstract. Postural reflexes act through a single excitatory motoneuron of the several that innervate a flexor muscle of the cockroach leg. A peripheral inhibitory neuron whose axon accompanies this excitatory motoneuron is able to suppress postural reflexes without affecting centrally generated muscle tensions. The inhibitory neuron could thus serve to rapidly suppress postural tensions at the initiation of escape.

Posture and locomotion are viewed as being programmed by the central nervous system and modulated by sensory feedback (1). Elements of central pattern generators for walking have been identified in vertebrates and invertebrates (2), but little is known about how postural reflexes interact with them. In rapid running, for example, such reflexes may be incompatible with centrally programmed locomotor patterns (3). Are these reflexes then suppressed or overridden?

We studied this problem in the American cockroach and found an effective mechanism for the rapid suppression of reflexly developed muscle tension through the action of inhibitory motoneurons at muscle cells.

The posterior flexor muscle of the trochanter (4) lifts the cockroach leg in support (5) and provides postural support when the animal is climbing or standing inverted (6). The nerve to this muscle contains at least 12 axons, but no more than four (axons 3, 4, 5, and 6) are active in quiescent or walking cockroaches (5). Each of these four motoneurons can be accurately identified in extracellular recordings (7). Axons 4, 5, and 6 are slow excitatory motoneurons that generate graded tension by facilitating depolarizing postsynaptic potentials (8). Axon 3 is a branch of the common inhibitory neuron that produces hyperpolarizing potentials in muscle cells and decreases the tension developed by the excitatory motoneurons (8).

Centrally generated patterns of activity in these motoneurons have been investigated. The common inhibitor (axon 3) and two excitors (axons 5 and 6) discharge regularly with the locomotor-like bursting seen in deafferented preparations. Nonsnipping interneurons that can generate these patterns and set a bursting rhythm have been identified; they affect only the same three flexor motoneurons (9). Axon 4 is only irregularly active in locomotor-like bursting.

Table 1. Axon 4 spikes in the flexor nerve with and without stimulation of the common inhibitor. Values are means ± standard deviations.

<table>
<thead>
<tr>
<th>Leg extension (degrees per second)</th>
<th>Axon 4 discharge (N = 4 (Hz))</th>
<th>Axon 4 discharge with common inhibitor stimulation (N = 3 (Hz))</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>8.2 ± 2.2</td>
<td>8.7 ± 2.8</td>
</tr>
<tr>
<td>150</td>
<td>63.6 ± 13.1</td>
<td>68.0 ± 14.6</td>
</tr>
</tbody>
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V. Linder and J. D. Rowley, Nature (London) 266, 744 (1977). Two patients with R2-21 variant translocations are described; in one, part of No. 13 is translocated to No. 21; and the end of No. 17 is translocated to No. 21.
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