During the past several years our group has focused on investigation of three human genes, ALL-1, hASH1 and ALR. The genes, which were cloned by us, are related in structure and function and have Drosophila homologues. The latter are termed TRX, dASH1 and M2B, respectively. Genetic analysis indicates that ALL-1, TRX and dASH1 are positive regulators of homeotic genes. The protein products of all the genes share motifs such as SET, PHD fingers and AT hooks (Figure 1). Such motifs have been found in a number of proteins involved in chromatin remodeling. In immunohistochemical analysis done with collaborators, the three Drosophila proteins were found at multiple discrete sites on polytene chromosomes. Moreover, TRX and ASH1 sites co-localized (Fig. 2), suggesting common targets, while M2B distributed at other sites. Within human cells, ALL-1, hASH1 and ALR proteins are visualized in intranuclear speckles and are present within distinct multiprotein complexes of ~2MDa. These complexes presumably play a role in targeting the proteins to the chromatin and/or in mediating their activity while bound to target genes. Currently, we are making a major effort to purify and characterize the ALL-1 complex. In the near future we will begin purification of the other two complexes. Finally, we are generating mice with mutations (conditional in ALL-1) in each of the three genes.

A second major direction in our laboratory has been the elucidation of the role of ALL-1 variants in human leukemogenesis. ALL-1 was cloned by virtue of its involvement in human acute leukemia, in particular infant and secondary leukemia. This occurs though chromosome translocations in which the N-terminal ~1400 residues of ALL-1 fuse in frame to the C-terminal segment of a "partner protein". Fifteen partner genes have been already cloned. Structural analysis indicates two pairs of highly related partner proteins (AF-9/ENL, AF-10/AF-17), but the rest are different. Unexpectedly, we found that in a significant number of acute myeloid leukemias, ALL-1 is rearranged through a different mechanism involving partial tandem duplication. This aberration results in production of a bigger ALL-1 protein.

We have recently applied the DNA microarray methodology to search for genes which are upregulated or downregulated in primary leukemias with the t(4:11) abnormality and the chimeric ALL-1/AF-4 gene. Analysis of ~10,000 human genes revealed 15 known genes which are upregulated by 3-27 fold in the t(4:11) tumors, compared to tumors with similar phenotype and surface markers which do not carry the aberration. Some of these genes are known to be overexpressed in other acute leukemias and others were previously found to be upregulated in hematopoietic stem cells or in other malignancies. We will now concentrate on utilizing mouse model systems, to try and show that overexpression of some of those genes indeed triggers leukemia.

Recent References


