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Genes Encoding the T-Cell Antigen Receptor

TAK W. MAK, NICOLETTE CACCIA, TAMMY COOK, VERONICA VADASZ, YASUNOBU YOSHIKAI, UIK SOHN, NOBUHIRO KIMURA, AND BARRY TOYONAGA

The Ontario Cancer Institute and Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

The search for the elusive and controversial T-cell antigen receptor is over. It is now clear that gene complexes for both alpha and beta chains are distinct from those for immunoglobulin genes. They are, however, related to Ig genes as well as to other class I and class II major histocompatibility complex (MHC) gene products. Therefore, they belong to the immunoglobulin super gene family.

The immune system consists of a complex assortment of cells and their products which provide specific and nonspecific protection against foreign agents. The specific immune response can be divided into humoral and cell-mediated responses. The humoral response, which provides protection against bacterial infections, is mediated by B lymphocytes and their antigen recognition product immunoglobulin [1,2]. The recognition of antigen initiates a series of acivation events, including interaction with specific helper T cells, that result in the morphogenesis of B cells into plasma cells. These plasma cells secrete large amounts of specific immunoglobulins into the circulatory system. The process by which immunoglobulin genes rearrange and express has been well-documented [1,2]. The cell-mediated immune response, on the other hand, is carried out by thymus-dependent or T lymphocytes. The functions of these cells are diverse. Helper T lymphocytes are able to enhance the response of both T cells and B cells, while suppressor T lymphocytes depress their response. Cytotoxic T cells are responsible for identifying and eliminating abnormal host cells, including those infected by virus and tumor cells that carry new and unusual antigens on their cell surfaces. Antigen recognition by T cells is mediated by a complex known as the T-cell antigen receptor (TcR). This receptor is a cell surface protein heterodimer composed of disulphide linked α and β chains [3–5]. For many years the molecular mechanism responsible for T cell recognition of antigen eluded investigation. In the past year, our laboratory [6,7] and others [8–11] have isolated the α and β chain of the TcR. This work has made it possible to study the structures of these molecules, the process by which diversity is generated, and TcR use in different T-cell subsets. T cells only recognize foreign antigens in the context of self-class I and class II molecules, encoded by the major histocompatibility complex (MHC) [12], a phenomenon known as MHC restriction. Intense interest is now directed towards the function of the T-cell receptor in MHC restriction. Other avenues of major interest will be the process by which the thymus selects for T cells that express receptor molecules capable of recognizing both antigen and MHC gene products, and whether the TcR plays a role in the development of T-cell malignancy.

Reprint requests to: Dr. Tak W. Mak, Ontario Cancer Institute, Department of Medical Biophysics, University of Toronto, 500 Sherbourne Street, Toronto, Ontario, Canada M4X 1K9.

Abbreviations:
C: constant
D: diversity
J: joining
MHC: major histocompatibility complex
TcR: T-cell antigen receptor
V: variable

ISOLATION OF A T-CELL ANTIGEN RECEPTOR cDNA

During the past year, our group and several other groups have been successful in isolating cDNAs that correspond to the α and β chains of the T-cell antigen receptor. Using the techniques of subtractive and differential hybridization, T-cell specific clones were produced using mRNA from T cells. The first successful isolations of the β chain of the human and mouse T-cell antigen receptor came from our group [6] and a group headed by Mark Davis [8], respectively. Subsequently, the isolation of the α chain by us [7] and others [9–11] have also been reported. It is clear that the genes coding for both the α and β chains of the T-cell antigen receptor are distinct from those of immunoglobulin. The finding that the human β chain is located on chromosome 7 where none of the Ig genes reside [13] confirms their distinction from these B-cell recognition proteins. The deduced protein sequence of these chains reveals that they are related to immunoglobulin, making them members of the immunoglobulin super gene family [14]. Detailed examination of the deduced protein sequences of these DNAs has revealed that the overall structure of these proteins may be similar to those of λ and κ immunoglobulin chains. In addition, the relative positions of the cysteine residues are similar to those found in the light chains of mammalian Ig molecules, which are known to be important for the inter- and intra-disulphide linking of the Ig chains. Sandwiched between the variable and constant domains of these T-cell proteins are amino acids which appear to be composed of diverse and joining segments, which correspond to those in immunoglobulin [6,8,15]. A stretch of nonhydrophylic amino acids is located at the C terminus of these polypeptides which presumably represents transmembrane portions of these proteins. The extreme carboxy ends are composed of short hydrophylic peptides which comprise the intra-cytoplasmic ends [6,7]. Thus, it would appear that the general organization and mechanism for the generation of diversity of these proteins may well be similar to those of Ig genes.

REARRANGEMENT OF T-CELL ANTIGEN RECEPTOR GENES

To form the mature T-cell receptor α and β chain molecules, a somatic recombination process must occur in these T cells, in a manner similar to those of Ig genes. This mechanism is required to provide the necessary diversity of these T-cell proteins. Using Southern gel analysis and radioactive cDNA probes derived from α and β chains of T-cell antigen receptor, it was demonstrated that somatic rearrangements of genes coding for these cDNA sequences occurred in thymic leukemic cells, as well as the 3 different T-cell subsets; helper, killer, and suppressor T cells [7,8,16]. Most of the rearrangements involve the so-called "looping" pattern—deletion of DNA segments between the V and D segments, as well as between the D and J segments. More complicated mechanisms such as what seem to be sister chromatid exchanges and the inversion of DNA segments have also been observed [17]. These results demonstrated that a process similar to the rearrangement of immunoglobulin molecules, also occurs in T cells and that the 3 subpopulations of T cells seem to use α and β receptor molecules encoded by the same gene families.

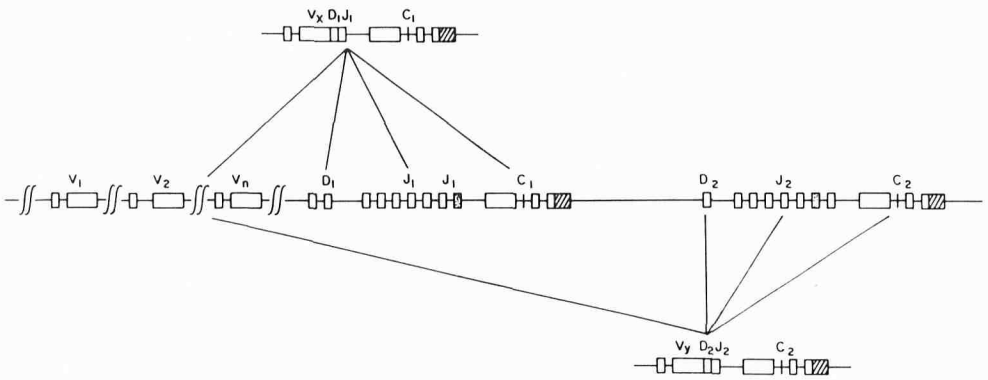

FIG 1. Genomic organization of the β chain T-cell receptor genes in germline DNA. *V*, variable; *D*, diversity; *J*, joining; *C*, constant. Numerical subscripts represent either the first or second gene cluster.

GENOMIC ORGANIZATION OF THE T-CELL ANTIGEN RECEPTOR GENES

The observation that sequences found in the messages encoded by the α and β chains are similar to those of Ig genes, and that they undergo somatic rearrangements in T cells [16] suggested that the general genomic organization of TcR genes must be similar to that of Ig genes. Although the genomic organization of the α chain is still not clear, that of the β chain has now been elucidated by several groups [15,18,19]. Their results demonstrated that these genes are encoded by a series of variable region genes, presumably followed 3′ by diversity (D) and joining (J) segments, and 2 highly homologous constant (C) region genes. These two C region segments appeared to have been duplicated together with the J-region genes, during the evolution of these genes, creating two clonally-related constant regions, each associated with a 5′ cluster of J-gene segments [15,18]. The D-region segments are located about 500–600 nucleotides 5′ of the J segments [20,21]. The genomic organization of the β chain gene is depicted in Fig 1.

In the T cells, this germline pattern is altered by recombination. First, a single D gene segment is brought into a position beside a single J gene and subsequently, a single variable (V) gene is transposed next to the combined DJ segment. In most cases, only after such rearrangement is it possible to produce a T-cell receptor α or β chain message, although a short β chain message composed of DJ and C regions can be detected in some cells. In the β chain, rearrangement can occur in both the first or second C region and use of either of these C regions is not correlated to any of the T-cell subsets. Through the use of multiple V, D, and J segments, it is possible to generate the required diversity of the T-cell receptor system.

EXPRESSION OF T-CELL RECEPTOR α AND β CHAIN GENES

In general, the transcription of T-cell receptor α and β chain genes is confined to cells from the T-cell lineage. The expression of these genes is found in cells from the thymus, as well as mature peripheral blood T cells with helper, killer, or suppressor properties [22]. In the case of the α chain messages, a message that is shorter than the full length mRNA can occasionally be found in B cells [7]. Since the rearrangement of these T-cell receptor genes occurs within the thymus, expression of mRNA corresponding to these genes can be detected in different subpopulations of thymocytes. For the β chain mRNA, a relatively high level can be detected during intrathymic differentiation which decreases about ten-fold in normal mature peripheral blood T cells [22]. The α chain message, on the other hand, does not appear to exhibit an elevated level in thymocytes. Two messages of different sizes can be detected in most immature T cells. In the case of β chains, they correspond to 1.3 kb and 1.0 kb messages. The longer message contains a complete V, D, J, C transcript [23]. A shorter message of 1.0 kb can also be detected in some immature leukemic T-cell lines, as well as thymocytes [22,23]. These mRNA lack the V region messages but contain either D, J, C [20,21] or occasionally simply J and C messages together with (intron) sequences 5′ of these D or J gene segments [23]. At least one β message has been found to lack a D region segment [23]. This optional use of D gene segment can presumably increase the diversity needed to encode receptors with various functions. Although 2 transcripts corresponding to 1.6 kb and 1.3 kb of the α chain message can also be detected [7], their compositions are not so clear. The longer message presumably encodes a complete V, D, J, and C message.

CONCLUSIONS

The search for the elusive and controversial T-cell antigen receptor is over. It is clear that the gene complexes for both the α and β chains are distinct from those of immunoglobulin genes. They are, however, related to Ig genes as well as to other class I and class II MHC gene products, making them part of the immunoglobulin super gene family. Their organization and mechanisms of recombination are also similar, but not identical, to those of Ig genes. With the search for the T-cell antigen receptor genes behind us, a new set of questions and goals lie ahead. In the next phase, we hope to address many controversial questions that remain to be answered. For example, how does the T-cell receptor, which is so similar to Ig recognize foreign antigens in association with MHC gene products? What is the mechanism for the production and selection of T-cell receptors that are tolerant to self antigens but, at the same time, recognize antigens in the context of self MHC gene products? What role does the thymus play in the selection of these T-cell receptors? Finally, what, if any, is the role of the T-cell receptor in T-cell-related clinical abnormalities such as T-cell neoplasias and autoimmune disease. With an intense effort devoted to understanding these problems, many of the answers will soon be forthcoming. One powerful approach will be to genetically reconstruct the α and β chains of T-cell receptors with specific functions to study the mechanism of recognition in isolation from other cellular determinants. The report on the reconstitution of an active T-cell receptor in human T cells by DNA transfer by Ohashi et al [24] could mark the beginning of such studies.

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