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THE REPERTOIRE OF GAMMA/DELTA TCR IN DROMEDARY IS DIVERSIFIED BY SOMATIC MUTATION AND CDR3 DIVERSIFICATION

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In Jawed vertebrates the T-cell immune response is mediated by the T-cell receptor ab or gd heterodimers, encoded by complex multigene families. The genetic information for these receptors is carried by a germline pool of variable (V), joining (J), diversity (D), and constant (C) genes that undergo somatic DNA recombination to generate receptors with diverse binding specificity. It has been suggested that the gamma/delta T cells represent a bridge between the innate and the adaptive immune systems. They show in fact unique features if compared with the more abundant alpha/beta T cells, e.g. a preferential distribution in epithelial and mucosal sites, and, in addition to the MHC-restricted one, an Ig-like antigen recognition mechanism. Diversity in receptor structure and mechanism of diversification is now being discovered in a lineage- and taxon-dependent manner, supporting the idea that metazoan immunity is an evolutionarily plastic system. Camelidae occupy a peculiar immunological niche within mammalians, since, in addition to conventional antibodies, the serum of these animals contains a significant amount of antibodies composed solely of paired H-chains (HCAbs). This feature, together with the phylogenetic placement of Camelidae among Cetartiodactyls, makes the study of the dromedary cellular immunity very intriguing.

We investigated T cell-mediated immunity in Camelidae, focusing on the TR delta (TRD) and TR gamma (TRG) repertoire in dromedary spleen. By a combination of 5'RACE and RT-PCR experiments, we first identified three TRDV subgroups and five joining (TRDJ) genes, and then two TRGV subgroups and two TRGJ genes. We provide evidence that the high diversity in sequence and length of the third complementarity determining region (CDR3) is a major component of TR delta and gamma chain variability. Moreover, comparison with the corresponding germline genes allowed us to show, for the first time in a mammalian organism, that productively rearranged TRDV and TRGV genes can undergo somatic mutation: the mutation rate per base pair is 0.013 (TRDV4 region) and 0.008 (TRGV1 and TRGV2 regions). A computational approach has been applied to determine the protein structure of the variable region of γδ heterodimers. The complex TRGV1-TRDV4 and TRGV2-TRDV4 were modeled on the human counterpart γδ TCR (PDB code: 3OMZ). From these structures it appears that solvent accessible surface area is higher in TRVG1 than in TRVG2 and this is due to different steric hindrance of the side chains mainly localized in the CDR region. It is possible that amino acid variations in gamma/delta T cells, which respond to antigens independently of antigen processing and MHC presentation, may be more easily

tolerated and maintained during evolution. This insight could be significant for understanding the evolution of the mechanisms generating diversity in the vertebrate immune system.