Diversity of Human αβ T Cell Receptors

Arstila *et al*. (*1*) estimated an average diversity of 9×10^5 different β chains and 4.5×10^5 different α chains in the human naïve T cell repertoire. To calculate the total T cell repertoire diversity, the β-chain diversity was estimated within a certain variable (V) gene family, $V_\alpha12^+$, comprising 2.5% of the total α-chain repertoire. Finding in this particular family an estimated total of 6×10^5 different β chains (i.e., two-thirds of the total β-chain repertoire), Arstila *et al*. suggested that the total T cell receptor (TCR) diversity comprises at least $(6 \times 10^5) \times 40 = 2.4 \times 10^7$ different αβ combinations (*1*). The authors acknowledge that this is only a lower bound, because the calculation assumes that the β chains that do bind at least one $V_\alpha12$ chain bind only one of the 4.5×10^5 different α chains in the $V_\alpha12^+$ family. If each β chain found within the $V_\alpha12^+$ family were to bind an average of *n* different $V_\alpha12$ chains instead, the total estimated TCR diversity would be *n*-fold higher than this lower bound.

Arstila *et al*. estimated an upper bound of 10^8 different αβ combinations (*1*). Pre–T cells having rearranged a β chain expand 1000-fold before the α chain is rearranged, and only 10% of these cells leave the thymus to enter the mature repertoire. Thus, it was argued that each β chain can maximally pair with any of about 100 different α chains.

This is indeed correct for all descendants of any particular pre–T cell having rearranged a particular β chain—but another pre–T cell rearranging the same β chain may bind to 100 different α chains. Thus, to calculate the upper bound on TCR diversity, one has to consider the frequency with which identical β-chain rearrangements are expected. This frequency can be estimated from the turnover rate of the naïve T cell repertoire. In human adults, the total body production of naïve T cells has been estimated at about 10^8 per day (*2*), a figure obtained from recovery rates following T cell depletion (*2*) and from an estimated 0.1% turnover (*3*) in a pool of 10^{11} naïve T lymphocytes. Assuming that most of this production is of thymic origin (*4*) and that more than 90% of the cells die before leaving the thymus (*1*), this implies a daily production of at least 10^9 pre–T cells. The 1000-fold expansion of the pre–T cells (*1*) before α-chain rearrangement implies that approximately 10^6 β chains should be made every day. Because this is close to the Arstila *et al*. estimate of total β-chain diversity, every β chain should be rearranged about every day.

Over the 1000-day expected life-span (*2*, *3*) of the progeny of a pre–T cell expressing a single β chain, therefore, 1000 recurrences of the same β-chain rearrangement might be expected. Hence, the upper bound for the total TCR diversity could easily be 1000-fold larger than calculated by Arstila *et al*. Such an upper bound, at 10^{11}, would allow almost every T cell in the naïve repertoire to have a unique TCR. The true TCR diversity may be several fold lower, however, owing to factors such as proliferation after the α-chain rearrangement and possible restrictions in αβ-chain pairing.

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Response: Keşmir *et al*. argue that although any developing TCR β chain will be paired at most with 100 different α chains, the same β chain may appear repeatedly and garner other sets of 100 α chains, increasing the total αβ TCR diversity from the 10^8 we estimated (*1*). We studied the diversity of the human αβ TCR in the blood of healthy adult donors at a given moment, not over time. Also, we did not measure the upper limit of α-to-β pairing; our estimate was based on what is known of αβ T cell development and TCR rearrangement. Thus, the comment of Keşmir *et al*. actually goes beyond our data.

Because any expansion after α-chain rearrangement will increase only clone size, not diversity, the argument of Keşmir *et al*. hinges on the assumption that the estimated total turnover of naïve T cells equals thymic production of pre–T cells. That assumption is incorrect, however, and ignores the well-documented role of post-developmental division in the maintenance of the naïve T cell population, especially in adults. Murine T cells may go through up to six cell cycles after α-chain rearrangement even before emigrating from the thymus (*2*). Haynes *et al*., cited by Keşmir *et al*., specifically argued for "minimal contributions of the thymus to maintenance or reconstitution of the peripheral pool of T cells . . ." in humans [(*3*), p. 457], and showed that the presence or absence of thymic function and even the surgical removal of the thymus had no impact on the reconstitution of the T cell compartment, including the naïve $CD4^+$ cells, in treated HIV-infected individuals. Naïve T cells, long after having completed TCR rearrangement, clearly have a considerable capacity for self-renewal.

The suggestion of Keşmir *et al*. can also be viewed as a question of clone size. If the size of the repertoire is 10^8 different TCRs, as we suggest, the average clone among 10^{11} naïve T cells would consist of 1000 cells, the progeny of a single intrathymic α-chain rearrangement after 10 cell cycles. These cycles should therefore be detectable in the naïve T cell population, and indeed this appears to be the case. Studying the disappearance of cells damaged by therapeutic irradiation, McLean and Michie (*4*) concluded that, on average, naïve T cells divide once every 3.5 years and die after 20 years, which suggests six post-thymic cell cycles in the life-span of an average naïve T cell. Other experimental approaches have suggested higher division rates. From age 25 to 70 years the mean telomere length in the naïve T cell population decreases from 9.5 kb to 8.0 kb, so an estimated loss of 50 to 100 base pairs (bp) per cell cycle translates to 7 to 13 divisions during the 20-year life-span of naïve cells (*5*). De Boer and Noest have argued that this estimate of telomere loss is too high; their estimate, 35 to 70 bp per cycle (*6*), would mean 10 to 19 cycles. At any given time the fraction of naïve T cells in cell cycle is 0.8% (*7*), which suggests a rate as high as one division per 125 days, or 60 cycles per life-span. The available data thus can easily accommodate 10 divisions producing the average naïve clone.

Studies on the frequency of antigen-specific T cell precursors provide an independent line of evidence that points to a diversity close to what we proposed. A conservative estimate of the frequency of such precursors in the naïve repertoire would be one per million; some studies have reported significantly higher frequencies (*8, 9*). Thus, a total repertoire of 10^8 TCRs would predict an epitope-specific response to consist of 100 clones, while Keşmir *et al*.'s repertoire of 10^{11} TCRs predicts a composition of 100,000 responding clones. The existing literature is more compatible with our prediction (*10–14*). Thus, we submit that the phenomenon that Keşmir *et al*. postulate, although in principle possible, has little impact on the total diversity.

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