Response to “Interaction between HIV gp41 fusion peptide and T cell receptor: putting the puzzle pieces back together”

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In his letter, Dr. Alexander Sigalov suggests an alternative interpretation to our results mapping the domain of FP1–32 that mediates the interaction with the TCR to the FP5-13 region (1). He suggests that, in addition to FP5-13, the C-terminus domain of FP1-32 contains a region capable of inserting itself into the membrane and interacting with the CD3 subunits of the TCR, thereby impairing TCR function. We consider this alternative explanation unlikely for several reasons. First, we have synthesized and investigated FP17-32 and found it inactive in all assays (unpublished data). Second, a mutant FP1-32 termed V2E shows a diminished ability to interfere with the activation of T cells both in vitro and in vivo (2), despite the fact that the mutation in V2E is located in the N-terminus and not in the C-terminus of FP1-32. Thus, if any inhibitory activity resides on the C-terminus of FP1-32, it must be secondary to the activity of the N-terminus. Thirdly, the current working model describing the mechanism of action of FP1-32 during membrane fusion in HIV infection suggests that FP1-16 inserts into the target T-cell membrane, while the FP17-32 region does not insert, but remains positioned parallel to the cell membrane (ref 1, Fig. 1) (3, 4). This positioning of the different domains of FP1-32 does not allow the FP17-32 region to insert into the membrane and interact with the CD3 subunits of the TCR complex as suggested by Sigalov.

The alternative interpretation suggested by Sigalov is based on the different potency manifested by FP1-32, FP1-16 and FP5-13 in Figs. 1 and 7 of our manuscript (1). However, a careful comparison of Figs. 1 and 7 reveals that FP1-32 and FP5-13 have similar inhibitory efficiencies; moreover FP1-32 and FP1-16 (Fig. 2) have similar activities in vivo. Thus, we attribute the differences in the efficiency of FP1-16 and FP1-32 not as an indicator of the existence of another independent inhibitory region, but as the result of the different solubility and state of aggregation of the different peptides; this effect seems to be more important for in vitro assays (Fig. 1), but less important for in vivo assays (Fig. 2). Indeed, FP1-32 is known to form oligomers (2, 4); this multimerization is facilitated by the C-terminus increasing fusogenic activity of FP1-32 (3, 4). Whether multimerization plays a role in the immunomodulatory activities of FP and its peptides is still unknown. Nevertheless, we believe that the above-mentioned data rule out the alternative interpretation put forward by Sigalov, that the C-terminus region of FP1-32 plays a significant role in its immunomodulatory activity.

REFERENCES


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doi: 10.1096/fj.07-0604ltr

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