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Perspectives

The Dawn of Quantum Immunology - ∂

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ABSTRACT

The molecular mechanisms underlying the intrinsic ability of T cell receptors (TCRs) to recognize a broad range of pMHC (peptide bound to molecules of major histocompatibility complex) ligands resulting in activation of only a subset of effector functions (partial or weak agonists) or in inhibition of the T cell's ability to respond to agonist stimulation (antagonists) has been the subject of much investigation. Thermodynamic and kinetic studies have been undertaken describing different T cell outcomes based on strength of signal of TCR-pMHC interaction. Nevertheless, the strength of signal has not been well defined and theories of how the biochemistry of pMHC interactions impact downstream immunological responses are all still debated as none of them explain all available experimental data. We have recently established that certain descriptors associated to the atomic structure of the peptide and its underlying electronic structure reflect the immunological outcome of the *in vitro* TCR-pMHC interactions. Our finding that atomic coordination is directly correlated to peptide immunogenicity represents the first example of a direct relationship between peptide atomic/electronic structure and TCR-pMHC functional avidity. The technological ability to define and predict peptide immunogenicity –particularly if this ability only involves some minimal determinism intrinsic to quantum mechanics– constitutes visionary science; such a possibility has far reaching implications, which transcend the TCR-pMHC complex and touch upon the generic issue of protein-protein interaction.

A key step of the adaptive immune response is the specific recognition by the T cell receptor (TCR) of foreign peptides bound to class I or II molecules of the major histocompatibility complex (peptide-MHC complex; pMHC) on the surface of antigen presenting cells. The type of the elicited immune response depends on the nature of the pMHC and the involved T cell [1]. Other not independently functioning signals via coreceptors, accessory and costimulatory interactions appear to increase the magnitude and/or the duration of TCR signals [2]. However, TCR-pMHC interaction is the decisive event that is required for all downstream events with respect to T cell response against foreign peptides.

Nevertheless, several studies have shown that individual TCRs really can recognize over a million different individual peptides in the context of a single MHC molecule [3-5]. Thus, on the contrary to what was initially suggested by clonal selection theory ("one-clonotype–one-specificity" [6,7]), TCRs are characterized by an extensive cross-reactivity (alternately referred as TCR degeneracy). This TCR paradox of exquisite specificity accompanied by marked cross-reactivity is of the utmost importance not only for immune defense but also for thymic selection, since, in order to differentiate in the thymus, T cells are also required to recognize with low affinity, MHC molecules bearing peptides derived from self-proteins [8,9].

Thus, the molecular mechanisms underlying the intrinsic ability of TCRs to recognize a broad range of pMHC ligands resulting in activation of only a subset of effector functions (partial or weak agonists) or in inhibition of the T cell's ability to respond to agonist stimulation (antagonists) [10-12] has been the subject of much investigation [13]. Since the first crystal structure determinations of TCR-pMHC complexes in 1996, structural, thermodynamic and kinetic studies have been undertaken describing different T cell outcomes based on strength of signal of TCR-pMHC interaction [2,14,15]. Nevertheless, the strength of signal has not been well defined and theories of how the biochemistry of pMHC interactions impact downstream immunological responses are all still debated as none of them explain all available experimental data [16-19]. All approaches which have attempted to address the TCR-pMHC structure-function relationship, including binding pocket energetics, molecular dynamics and thermodynamical modelling have been proven to be prone to extensive binding/free energy degeneracy, evidently failing altogether to yield accurate prognostic models of the TCR-pMHC outcome.

The atomic or the electronic scale of protein-protein interaction is invariably intractable for biologically relevant structures. On the other hand, the existing gap in understanding the apparent paradox of TCR specificity and cross-reactivity may be attributed to the unavoidable referencing at the mesoscale (of the order of 100 Å in the case of the TCR-pMHC complex) as is, for instance, the norm in kinetic studies via molecular dynamics. Such approach, however, apparently reflects primarily the technical conundrums rather than a conscious research choice; the issue of relating the electronic state of the TCR-pMHC complex to any plausible biological mechanism operating on the molecular level requires cross-discipline skills and cross-discipline intuition, which, even today, represents a challenge. In other words, it is understandable that reverting to the mesoscale is owing to the appreciable span of length scales –between three and four orders of magnitude– which separates the molecular level of the immune recognition from any causal mechanism [20] at the atomic level of protein structure. However, the indications that such a relation may be convincingly decrypted have already been in place since the substitution of a single peptide residue is able to alter the functional outcome of TCR-pMHC recognition. The latter behaviour must be seen as reflective of the causality cast upon a scale smaller than the residue (e.g. on the electron density).

On this basis, we have recently established that certain descriptors associated to the atomic structure of the peptide and its underlying electronic structure reflect the immunological outcome of the *in vitro* TCR-pMHC interactions [20-24]. This finding was initially arrived at by addressing the case of the Tax nonapeptide (LLFGYPVYV) from the human T-cell leukemia virus type 1 (HTLV-1) that, presented by the HLA-A0201, acts as a strong agonist for the A6 TCR [25]. Most profoundly, while laying out our methodology, we contemplate that the study of the electronic structure of the TCR-pMHC interaction opens up a whole new field of research, which may qualify as Quantum Immunology.

Within the premise of our studies a combination of atomic correlation statistics (primarily atomic coordination, to be also referred to as coordination henceforth) and quantum chemical calculations were shown to predict immunological responses [21-23]. More precisely, our work on the Tax protein [26-28] indicated that a number of Tax variant peptides (which present spectacular differences in functionality, while exhibiting near-identical stereochemistry [25]) in complexation with the same TCR, consistently revealed different quantum chemical behavior, intrinsically expressed by the protonation state of the peptide's N-terminus [22]; agonist peptides selectively exhibited a stable ammonium group on their N-termini, which was altogether unattainable for antagonists. Remarkably,

this finding was consistent across the range of conditions studied in regard to peptide formal charge and protonation of side chain groups [22,23]. Most importantly, the difference in the quantum chemical behavior of agonists versus that of antagonists was found to be reflected on the coordination of the variant in respect to the native (index) peptide: over-coordination in respect to the index signified an agonist, whereas under-coordination indicated an antagonist. It was additionally established that this trend is also valid for all crystallographed variants of the immunodominant human cytomegalovirus (HCMV) peptide (NLVPMVATV, $pp65_{495-503}$) [24].

The results in Figure 1 are dependent on a single peptide structure for each of the Tax variants studied. The peptide structures were determined by previous crystallography studies. For each of the crystallographed structures, quantum mechanical relaxation of the H species resulted in a number of differing conformers. However, the heavy atoms on all conformers were kept immobile in their original (crystallographed positions). In order to test the potential for generalization of these results, we additionally performed classical molecular dynamics (MD) studies in which each of the crystallographed structures was introduced to thermal motion at physiological conditions. All MD simulations were performed in the micro canonical ensemble (NVE). Based on our unpublished data, the distribution of the antagonist P6A was shifted towards lower coordinations in respect to Tax confirming the trend of agonist under-coordination shown in figure 1.

The emerging tight link between the peptide-specific T cell response and the atomic coordination of peptide's tertiary structure is of the utmost importance. Its confirmation would provide

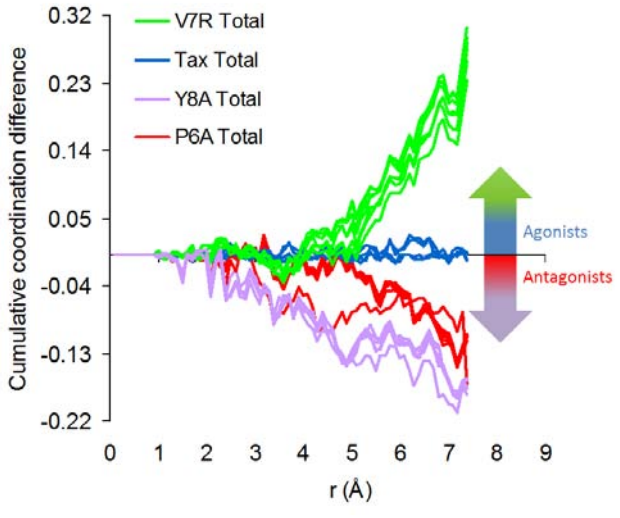

Figure 1: Atomic coordination correlates to peptide functional avidity. Each line represents the coordination difference of a Tax peptide variant in respect to the charge-neutral Tax peptide (index). Coordination differences were calculated for the P6A (antagonist), Y8A (weak antagonist/null) and V7R (weak agonist) variants. Calculations involved a number of Tax peptide conformers, for a range of formal charges and electron spin polarizations (the latter was considered to be induced by an external stimulus). All differences refer to total coordination (i.e. that arising from interatomic interactions irrespective of atom species). All calculations were based on the tertiary structures of the peptides as these were extracted from TCR-pMHC crystallographed complexes deposited in the Protein Data Bank (PDB); for PDB accession codes and methodological details the reader is referred to our original publications [21,23,24]. Calculations of PDF, RDF and of coordination numbers were performed with the PRDF program [29-31].

explanation for the dependence of the immune response on the primary structure of the peptide. Furthermore, it may constitute the scientific underpinning of the ability to manipulate immune responses based on the principles of quantum mechanics. It should be stressed that atomic coordination is essentially a high-level abstraction of electronic structure and, in particular, of the manner in which valence electrons combine towards the formation of molecular orbitals (i.e. of covalent bonds). The types of chemical bonds and their strength when valence electrons combine depends principally on the types of atoms within the first coordination shell of interatomic interactions. This fact is particularly important in the case of peptide structure as the first coordination shell is principally dictated by the primary sequence of the peptide. Hence, it could be said that primary structure feeds into the electronic structure by means of coordination and it is more than likely that, in the case of the peptide, this relation will eventually be accurately simulated by quantum molecular dynamics. For that to happen with adequate consistency, the mechanism of quantum confinement of the peptide on the MHC groove must be previously uncovered. We envisage that atomic coordination may be used as a cost function for the determination of such peptide confinement and we deem that our current work is the precursor of *in silico* synthesis of the tertiary structure of peptides as a dependable alternative to crystallography.

We argue that there must be a fundamental (i.e. based on electronic structure) mechanism underlying even to the kinetics of the peptide during TCR recognition, albeit potentially a complex one. Although quantum molecular dynamics in the Born-Oppenheimer regime may provide intuition as to the kinetics, the normal practice is to reference the energetics of peptide binding into MHC pockets; however this practice has not managed to account for any fundamental mechanism common to all crystallographed peptides. On the contrary, atomic coordination of peptide tertiary structure in the pMHC-TCR complex appears to be the definitive functional descriptor for the discrimination of peptide agonism. Again, the research theme of merit, according to our current understanding, is the assessment of the role of pMHC rigidity – and the implication of hydrophobic portions of the peptide in this rigidity – in the functional outcome; on the basis of atomic coordination this research theme may be resolved quite soon.

Our finding that atomic coordination is directly correlated to peptide immunogenicity represents the first example of a direct relationship between peptide atomic/electronic structure and TCR-pMHC functional avidity. Accordingly, the technological ability to define and predict peptide immunogenicity –particularly if this ability only involves some minimal determinism intrinsic to quantum mechanics– constitutes visionary science; such a possibility has far reaching implications, which transcend the TCR-pMHC complex and touch upon the generic issue of protein-protein interaction. In the same context, the ability to predict peptide immunogenicity sets the scene for unprecedented technological possibilities.

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