Journal of Pulmonary Medicine

Commentary

A SCITECHNOL JOURNAL

Molecular Dynamics at the Checkpoint

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Abstract

Computational molecular dynamics and by big data analysis disclose molecular movement patterns relevant for drug development and function. Atoms in the contact zones of the PD-1 receptor move differently depending on the binding partner: the natural ligand, PD-L1, or the checkpoint inhibitors nivolumab and pembrolizumab, respectively. Computational analysis was performed by an interdisciplinary team from MedUni Vienna and the University of Natural Resources, Vienna. The natural ligand, PD-L1, not only binds but also activates PD-1, thereby inducing T-cell apoptosis. Cancer cells may, by expressing PD-L1, halt natural immune attack and thus survive. Checkpoint inhibitors are designed to just bind to PD-1, but without activating it. This functional difference is reflected by molecular movements analyzed in the papers by Roither being outlined here.

The Method of Molecular Dynamics

Molecular dynamics is a computational technique to compute atomic movements similar to a planetary system – but for thousands of atoms rather than nine planets. Atomic positions of all molecules (PD-1,PD-L1, nivolumab, pembrolizumab) are taken from the Protein Data Bank (PDP) [1-4] (Figure 1). Given positions, distances and forces between atoms are computed [5]. Atomic velocities are assigned randomly, according to physiological temperature. The, flight trajectories are then computed along a very short interval of time (2 × 10-15 sec), yielding the next configuration, i.e. new positions, distances, forces and velocities. The next step of simulation may follow [6]. The system can be watched just like in a movie. At intervals, positions are stored and represent a 'trajectory' for subsequent evaluation.

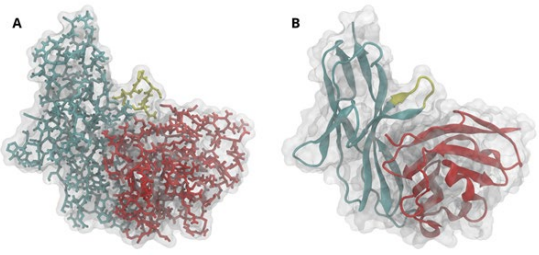

Figure 1: PD-1_{PD-L1}: PD-1 together with ist natural ligand PD-L1. CC'-loop, at the interface towards the ligand, colored yellow. (A) ‚bonds'-representation. (B) ‚cartoon'-representation.

The software GROMACS [7,8] was run on the supercomputer at the Vienna Scientific Cluster (VSC) and took 5 weeks to compute the system's development during a real time of 200 nanoseconds.

Refined Big Data Analysis

Advanced analysis is mandatory to extract anything meaningful from the vast amount of data. For evaluation, the software Visual Molecular Dynamics (VMD) [9] and programs coded in MATLAB [10] were used.

Similarity and Clusters

In a first step, configurations are compared and considered similar if their multidimensional distances [11] are small. Multidimensional distance may be defined across a whole molecule or with respect to some special part, such as an alpha helix, a beta sheet or a loop. Similar configurations may be grouped into clusters [12]. In our system, the CC'-loop of PD-1 (Figure 1) proved a most relevant region for clustering.

Clusters Relate to Function

Certain clusters regarding the configuration of the CC'-loop occur with both, the natural ligand as well as the drugs as binding partner. Other clusters occur with specific partners only. For example, one specific configuration of the CC'-loop is only seen with Pembrolizunab as ligand- it is 'specific'for this drug. Conversely, with the natural ligand, the very same loop toggles between two configurations (clusters), (Figure 2). This may represent the molecular reason why the natural ligand is able to trigger PD-1 while the drug does not – it just binds and blocks the checkpoint [13-15].

Conclusion

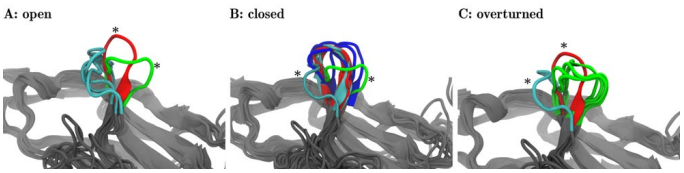

Figure 2: Fleur-de-CC' – Upon pembrolizumab binding the CC'-loop blooms. Depending on the binding partner, the CC'-loop assumes diferent conformations: 'open' (A) 'closed' (B) 'overturned' (C). Reproduced from[2].

Molecular dynamics simulation offers detailed insight into basic mechanisms of molecular medicine and is a conerstone of in silico drug design. It reveals atomnistic explanations that cannot be povided experimentally, regarding biololecules and also drugs. Nivolumab and Pembrolizumab have already been evaluated regarding lung cancer. Modified drugs may be simulated to estimate their therapeutic potential prior to wet lab or even clinical studies. While the described article focuses on PD-1, other chekpoints and corresponding inhibitors may be tackled as well using the very same techniques opening a wide range of applications of Computational Molecular Medicine.

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Received Date: 16 August, 2021; **Accepted Date:** 30 August, 2021; **Published Date:** 06 September, 2021

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