

## 拟提名 2024 年度云南省科学技术奖励项目公示

**项目名称:** HIV-1 包膜蛋白 gp120 构象调控的分子机制

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**提名奖别:** 云南省自然科学奖三等奖

### 项目简介:

获得性免疫缺陷综合症, 俗称艾滋病, 由人类免疫缺陷病毒 (Human Immunodeficiency Virus, HIV) 感染引发, 是一种严重危害人类健康的传染性疾病。HIV-1 包膜蛋白 gp120 在病毒入侵细胞和对宿主免疫反应的逃逸中发挥着关键作用, 因此成为开发抗病毒药物和疫苗的关键靶点。通过识别并结合宿主细胞表面受体 CD4 和辅助受体, gp120 通过一系列构象改变介导了病毒入侵细胞的关键步骤。面对宿主免疫系统所施加的选择压力, gp120 进化出高度的序列多态性和结构可变性以逃避中和抗体的识别和攻击。尽管人们已对 gp120 进行了深入的序列和结构分析, 但其与细胞入侵和免疫逃逸相关的构象变化的调控机制还不明确。我们在国家自然科学基金、云南省科技计划等 7 个项目的支持下, 使用多学科交叉手段, 较为系统地研究了 HIV-1 包膜蛋白 gp120 构象调控的分子机制, 取得了以下重要科学发现:

(1) 揭示了 gp120 末端构象间的动态平衡是决定病毒中和表型的分子基础。发现 gp120 在开放 (open) 和关闭 (closed) 两种末端构象之间维持着动态平衡, 不同 HIV 分离株的平衡模式与其中和表型密切相关。通过构象群体分布和构象状态转换的定量分析, 证实 gp120 末端构象间的动态平衡是决定病毒中和表型的分子基础。

(2) 阐明了 CD4 结合影响 gp120 构象转换的热力学机制。通过模拟孤立 gp120 从关闭态转换到开放态的原子分辨率转换过程, 揭示了 gp120 的构象转换本质上是一种自发性的动态行为。发现了 CD4 会选择性地结合 gp120 构象转换过程的适合状态, 并通过空间位阻效应阻止其向非活性关闭态的转换。

(3) 开发了定量描述蛋白质动力学、构象状态分布和构象转换的计算方法。通过将分子动力学模拟和深度学习相结合, 开发出了适用于蛋白质结构动态性、构象柔性、分子运动模式分析以及自由能谱重构和分析的计算方法, 并应用于抗 HIV 药物再利用、冠状病毒刺突蛋白与受体结合亲和性, 以及极端温度蛋白酶温度适应性等相关研究中。

以上研究结果在物理化学 TOP 期刊 *Phys. Chem. Chem. Phys.*、生物化学与分子生物学 TOP 期刊 *Int. J. Mol. Sci.*、物理化学 BBA 系列期刊等蛋白质研究权威 SCI 刊物上发表。20 篇核心论文全部为 SCI, 累计影

响因子 72.84, SCI 他引 1079 次, ESI 高被引论文 2 篇, TOP 期刊 12 篇, 封面论文 1 篇。发表论文被权威学术论文引用和评述。主编出版相关专著 1 部。7 名主要完成人中, 4 名入选云南省“兴滇英才支持计划”青年人才、1 名入选中科院“西部之光”访问学者。形成了以蛋白质为主要研究对象的生物学、计算机科学交叉学科的省级创新团队。

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