Proteolysis targeting chimera

A **proteolysis targeting chimera** (**PROTAC**) is a heterobifunctional small molecule composed of two active domains and a linker capable of removing specific unwanted proteins. Rather than acting as a conventional enzyme inhibitor, a PROTAC works by inducing selective intracellular proteolysis. PROTACs consist of two covalently linked protein-binding molecules: one capable of engaging an E3 ubiquitin ligase, and another that binds to a target protein meant for degradation. Recruitment of the E3 ligase to the target protein results in ubiquitination and subsequent degradation of the target protein by the proteasome. Because PROTACs need only to bind their targets with high selectivity (rather than inhibit the target protein's enzymatic activity), there are currently many efforts to retool previously ineffective inhibitor molecules as PROTACs for next-generation drugs.[1]

Initially described by Kathleen Sakamoto, Craig Crews and Ray Deshaies in 2001,[2] the PROTAC technology has been applied by a number of drug discovery labs using various E3 ligases,[3] including pVHL,[4][5][6] Mdm2,[7] beta-TrCP1,[2] cereblon,[8][9] and c-IAP1.[10] Yale University licensed the PROTAC technology to Arvinas in 2013–14.[11][12]

Mechanism

Protacs achieve degradation through "hijacking" the cell's Ubiquitin–Proteosome system (UPS).[13] The UPS consists of an E1 activating enzyme which conjugates to an E2 enzyme transferring a ubiquitin molecule to the E2. E2 then binds to the E3 ligase in a complex which can then recognize target proteins for subsequent ubiquitin tagging and degradation by the 26S proteosome.

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