Cutting Edge View

Lessons Learned Fighting HIV can be Applied to Anti-Cancer Drug Design

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KEY WORDS

Introduction of a number of HIV-1 protease (PR) inhibitors as anti-AIDS drugs has drastically changed the clinical prognosis for the outcome of this disease, from almost invariably lethal to chronic. This achievement also represented the first major success of structure-based drug design, encouraging the use of similar approaches to other major diseases, such as cancer. We have now identified adult T-cell leukemia (ATL) as a possible target for a similar treatment.

It is now accepted beyond a doubt that a number of cancers are caused by viruses, and by retroviruses in particular. It had been shown already 25 years ago that human T-cell leukemia virus type 1 (HTLV-1) is epidemiologically associated with ATL[1] and the current estimate is that up to 30 million people world-wide are infected with HTLV-1. Such infections are particularly prevalent in Japan,[2] and for the fraction of infected individuals who actually develop ATL, no efficacious treatment is available.[3] We postulate that designing inhibitors for HTLV-1 PR may represent a new way of preventing and/or treating ATL.

HTLV-1 is a retrovirus that is in many respects similar to HIV-1. In particular, both viruses encode a protease necessary for their maturation. Although the enzymatic properties of HTLV-1 PR have been already studied in some detail,[4] no three-dimensional structure of this enzyme was available until now. The dearth of structural information hindered the design of inhibitors using the principles of rational drug design, so elegantly and successfully applied in the case of HIV-1 PR.[5] Moreover, the existing anti-HIV-1 PR inhibitors turned out to be ineffective against HTLV-1 PR. This is not surprising in view of the low (27%) sequence identity and of the documented different substrate specificities of the two enzymes. These observations punctuate the notion that accurate targets are required for successful design of drugs. Their structures need to be defined experimentally at the atomic level by either crystallography or NMR.

With this objective in mind, we have recently solved the crystal structure of HTLV-1 PR[6] in complex with a specific inhibitor which mimics an efficiently processed substrate of this enzyme. As expected, the overall fold of HTLV-1 PR is similar to that found in other retroviral proteases, including HIV-1 PR. Specifically, the enzyme is a pseudosymmetric homodimer composed of two identical subunits, which interlace their termini in a β-sheet interface supporting the active site formed by two aspartate residues. Two extended flap arms protect the substrate-binding cavity from the other side and contribute one-half of the residues responsible for substrate/inhibitor recognition. Since the flaps have a unique conformation in HTLV-1 PR, their proper modeling is essential for successful design of HTLV-1 PR specific inhibitors. The inhibitor is bound in an extended conformation typical for other peptidic and peptidomimetic ligands bound to retroviral proteases, and each carbonyl oxygen and amide group of its backbone participates in direct hydrogen bonds with the enzyme as in other retroviral proteases. However, significant differences are seen in some of the pockets that accommodate the inhibitor side chains. These differences explain why various anti-HIV drugs in current clinical use, such as amprenavir, saquinavir, indinavir, ritonavir, and nelfinavir, fail to inhibit HTLV-1 PR,[7] and suggest the chemical and steric prerequisites of an optimal inhibitor. We found that two residues, Trp98 and Leu57 of HTLV-1 PR, are particularly responsible for the specific requirements of HTLV-1 PR (Fig. 1). It is clear that the future inhibitors of HTLV-1 PR may need to be considerably different as compared to either the currently available drugs targeting HIV-1 PR, or even novel HIV-1 PR inhibitors that are being introduced in order to overcome multi-drug resistance. For instance, the larger binding pockets S2 and S4 in HTLV-1 PR are more suitable to accommodate medium-sized hydrophobic residues, whereas the corresponding sites of the specific substrates of HIV-1 PR typically contain residues with small side chains, such as Ala or Asn in the P2 position, and hydrophilic Ser or Thr in P4. These preferences will impact the design of inhibitors.
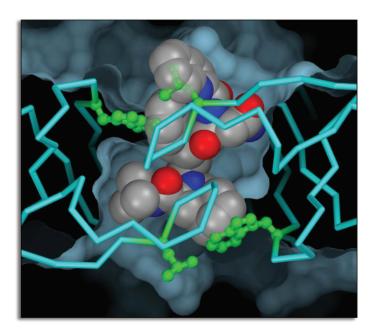
Figure 1. Anti-HIV drug saquinavir modeled into the active site of HTLV-1 PR. The drug molecule is shown in a space-filling representation with carbon atoms colored gray, oxygen red and nitrogen blue. Partially cut-away surface of the active site cavity of the enzyme is shown in light blue, together with the tracing of the relevant parts of the main chain of the protein. Side chains of the residues that are clashing with the drug are shown in green. Image prepared by Dr. David Goodsell using the Python-based Molecular Viewer.

Further Reading
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The study provides the necessary first step for future structure-based design of novel inhibitors of HTLV-1 PR, but is by no means complete. It will be still necessary for rapid progress in future studies to overcome the propensity of the protein to aggregate and the present structure will serve as a guide to surface mutations to alleviate that problem. We found that some surface residues, (for instance, Phe80), might create hydrophobic patches, stimulating aggregation also in the crystal.[8] Mutation of such residues should remove these sticky patches and decrease the propensity for aggregation. We also hope that, as was the case with HIV-1 PR, the availability of atomic coordinates of the target enzyme will excite the interest of pharmaceutical companies in developing anti-cancer drugs for the treatment of HTLV-1 induced ATL. The extensive experience gained from utilization of protease inhibitors as anti-HIV drugs,[5] coupled with the observations that antiviral compounds appear to provide therapeutic benefits for the treatment of pathological conditions caused by HTLV-1,[2] bode well for the practical utilization of this novel drug target.