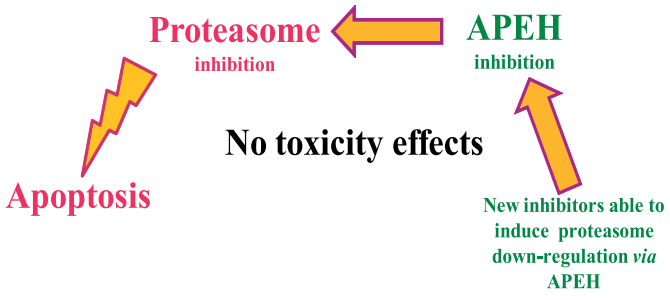
M. Saviano,[a] E. Langella,[b] M. Gogliettino,[c] P. Bergamo,[d] M. Ruvo,[b] A. Sandomenico,[b] M. Rossi,[c] and G. Palmieri,[c] *[a]IC-CNR Via Amendola, 122/O BA, (Italy). [b]IBB-CNR Via Mezzocannone, 16 NA, (Italy). [c]IBP-CNR Via P. Castellino, 111 NA, (Italy). [d]ISA CNR Via Roma AV, (Italy).* E-mail: michele.saviano@ic.cnr.it

A Sulfolobus solfataricus acylpeptide hydrolase (APEH), named $APEH_{Ss}$ has been identified and characterized. The protein is the endogenous protease target of the already isolated inhibitor SsCEI [1]. APEH is one of the four members of the prolyl oligopeptidase family, which removes acylated amino acid residues from the N terminus of blocked oligopeptides. SsCEI is the first protein able to efficiently inhibit APEH from mammalian sources with IC_{50} values in the nanomolar range. The 3D model of $APEH_{Ss}$ alone or in complex with SsCEI has been proposed, suggesting an inhibition mechanism of steric blockage on substrate access to the active site or on product release [2]. Interestingly, the identified reactive site loop (RSL) of SsCEI includes an unusual amino acid sequence which cannot be classified in any of the canonical motifs of serine protease inhibitors so far characterized. Therefore, a number of small peptides has been designed and synthesized on the basis of the RSL sequence. They are surprisingly stable and highly structured in aqueous solutions and show inhibitory activity against *S. solfataricus*, and human APEHs with IC_{50} values in the order of low micromolar. In light of a recently proposed cooperative role for the APEH–proteasome enzymatic system in controlling protein turnover, we investigated the proteasome down-regulation *via* APEH inhibition, hypothesizing that APEH can be used as a new target to indirectly control/modulate proteasome functions in tumoral cells. We identified different compounds that induce proteasome down-regulation *via* APEH, in both cell-free and cell-based assays. These molecules efficiently down-regulated human APEH activity in a dose-dependent manner in the human colon carcinoma cell line (Caco-2 cells) or in the baby-hamster-kidney (BHK) cell line, without any toxic effects and inducing proapoptotic and antitumoral effects. Surprisingly, in both cell lines such molecules markedly reduced the proteasome activity with a concomitant accumulation of several known cytoplasmic proteasome substrates. Furthermore, a molecular docking analysis has been carried out to assess the potential enzyme binding sites involved in the APEH–inhibitors interactions.

These results represent a starting point for a promising strategy in cancer therapy involving a new class of molecules for proteasome down-regulation mediated by knock-out of APEH activity.



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Structural basis for floral induction by rice florigen Hd3a

Izuru Ohki,[a] Kyoko Furuita,[a] Kokoro Hayashi,[a] Ken-ichiro Taoka,[b] Hiroyuki Tsuji,[b] Atsushi Nakagawa,[c] Ko Shimamoto,[b] Chojiro Kojima,[c] *[a]Laboratory of Biophysics, Graduate School of Biological Sciences, Nara Institute of Science and Technology, [b]Laboratory of Plant Molecular Genetics, Nara Institute of Science and Technology, [c]Institute for Protein Research, Osaka University,* E-mail: i-ooki@bs.naist.jp

Florigen is a hypothetical leaf-produced signal that induces floral induction at the shoot apex. The nature of florigen has remained elusive for more than 70 years. But recent progress toward understanding the molecular mechanism for flowering in *Arabidopsis* has led to the suggestion that FLOWERING LOCUS T (FT) is the mobile flower-inducing signal. Actually, the protein encoded by Hd3a, a rice ortholog of FT, moves from the leaf to the shoot apex and induces flowering in rice [1]. The floral transition by the FT or Hd3a protein is achieved by transcriptional activation of floral genes at the shoot apex, however, the molecular mechanism remains unclear. To understand this mechanism, we performed a structural analysis of the rice florigen Hd3a.

The polypeptide encoding the rice florigen Hd3a was expressed in bacterial cells with a novel high-level bacterial expression system pCold-GST [2]. The crystal structure of Hd3a was determined. Hd3a-interacting proteins were identified by Yeast Two-Hybrid and evaluated interactions with Hd3a by NMR titration experiments, isothermal titration calorimetry (ITC) measurements and GST-pull down assay. From these results, the molecular mechanism of floral induction by florigen will be discussed.

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Crystal structure of human importin-α (Rch1)

Hideyuki Miyatake,[a] Akira Sanjoh,[b] Go Matsuda,[a] Yuko Tatsumi,[b] Naoshi Dohmae,[a] Yoko Aida[a] *[a]RIKEN Advanced Science Institute, 2-1 Hirosawa, Wako-shi, Saitama 351-0198 (Japan). [b]Protein Wave Corporation, 1-7 Hikaridai, Seika-cho, Kyoto 619-0237 (Japan).* E-mail: miyatake@riken.jp

Importin α is involved in a variety of nuclear transport processes of external viral proteins responsible for the infection. To elucidate structural basis of viral infection responsible for the transport mechanism of viral components across the nuclear membranes, we carried out structural study of the major variant of the human importin α, Rch1. We truncated the N-terminal of the Rch1, and then could crystallize the IBB (importin β binding domain) truncated mutant of Rch1 (ΔIBB-Rch1) by the vapor diffusion technique. We collected X-ray diffraction data of the ΔIBB-Rch1 using the mail-in system [1] operated in SPring-8, Japan. The ΔIBB-Rch1 crystallized in space group $P4_32_12$ with cell dimensions of $a=b=139.10$ Å $c=140.96$ Å. We solved the crystal structure by the molecular replacement technique using human importin α5 as a template structure. The resultant structure of ΔIBB-Rch1 formed a tightly bound homo-dimer in the right-handed super-helical manner. Each protomer of the dimer consists of ten ARM repeats, where the ARM1 and ARM5 is the major dimerization region. The region corresponding to the typical NLS binding sites are