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Letters to the Editor / Cartas al Editor

APPLYING THE RESONANT RECOGNITION MODEL TO PR20, A "PECULIAR" HIV PROTEASE ESCAPE MUTANT: EXPERIMENTALLY REPORTED AND THEORETICALLY PREDICTED ACTIVITY CHANGES.

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To the Editor:

The Resonant Recognition Model (RRM) is a physico-mathematical approach with a different insight into bio-macromolecules[1-2]. As stated by Ho, "The real bioinformatics revolution may be here, not the one hyped in mainstream science journals, nor the 'systems biology' supposed to make intellectual meat out of genome sequences 'blasted' in and out of databases with little success so far. It is something else, and the scientists at the heart of it started by asking a question that was unthinkable except to a very few: Is it possible that molecules recognize and find each other by singing the same note(s), or flashing the same color(s)?[3]."

Besides being deeply theoretical, RRM provides answers to diverse practical questions, as accurately predicting the outcome of a mutagenesis experiment[4].

In RRM, a protein's sequence is represented as a numerical series of electron pseudo-potentials, each value corresponding to the value of pseudo-potential for the corresponding aminoacid. Numerical series are converted into spectra and consensus spectra are found for groups of orthologous proteins. Consensus spectrum is obtained through cross-multiplication of individual spectra. According to RRM, similar proteins have at least one common "resonant" frequency. There is mounting experimental evidence supporting the biophysical meaning of the resonant frequency as an individual protein's hallmark for its interaction with substrates and other proteins.

Recently, we published the results of a Resonant Recognition Model (RRM) study of the HIV protease[5]. In our study, two relevant frequencies were found in the HIV protease consensus spectrum: f= 0.0586 ± 0.004, putatively associated to proteolytic activity; and f=0.1797± 0.004, reflecting the general activity of the HIV virus. A part of that paper was devoted to compare theoretical predictions of several point mutations on catalytic activity (assessed by relative change in the spectral vale for f=0.0586) with literature reports on measured proteolytic activity.

We found that in 28 documented single-point mutations, correspondence between theoretical prediction and experimentally reported catalytic activity was confirmed for 26 of them (93%).

It is known that HIV protease has a tremendous capability to display multiple mutations while keeping proteolytic activity and reducing affinity for therapeutic protease inhibitors.

We believe that there is enough evidence for using RRM as a tool for predicting the effect of different HIV protease mutations on proteolytic activity.

Here we tried to theoretically "predict" the effect on proteolytic activity of PR20, an unusual protease "escape" mutant purportedly having 20 single point mutations respect to the standard HIV protease (PR).

According to the authors of[6], this escape mutant of HIV-1 protease (PR20) undergoes efficient polyprotein processing even in the presence of clinical protease inhibitors. PR20 shows >3 orders of magnitude decreased affinity for protease inhibitors darunavir and saquinavir relative to PR.

Other authors[7], reported that mature PR20 is catalytically competent with a similar turnover rate (Kcat) and an approximately 13-fold higher (Michaelis constant) Km for a synthetic substrate relative to PR.

On the other hand authors of[6], found a 10 fold reduction in catalytic activity of PR20 (apparently due to an increase in Km), even when these results were no consistent with the fact that PR20 is capable of autocatalytic processing (in spite of the presence of inhibitors) to produce viable virions.

In table I, the primary structure of both PR and PR20 are represented.

Table I. HIV protease primary sequences for PR (upper row) PR20 (middle), and Cam2 (down).
The corresponding mutations of PR20 are highlighted (Purple respect to PR, red respect to Cam2 and green respect to both).

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
P	Q	I	T	L	W	Q	R	R	L	V	T	I	K	I	G	G	Q	L	K
P	Q	I	T	L	W	K	R	P	F	V	T	V	K	V	G	G	Q	L	K
P	Q	F	S	L	W	K	R	P	V	V	T	A	H	I	E	G	Q	P	V
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
E	A	L	L	D	T	G	A	D	D	T	V	I	E	E	M	S	L	P	G
E	A	L	L	D	T	G	A	D	N	T	I	F	E	D	I	N	L	P	G
E	V	L	L	D	T	G	A	D	D	S	I	V	A	G	I	E	L	G	S
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
R	W	K	P	K	M	I	G	G	I	G	G	F	I	K	V	R	Q	Y	D
R	W	K	P	K	M	V	G	G	I	G	G	F	L	K	V	R	E	Y	D
N	Y	S	P	K	I	V	G	G	I	G	G	F	I	N	T	K	E	Y	K
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Q	I	I	I	E	I	A	G	H	K	A	I	G	T	V	L	V	G	P	T
Q	V	P	I	E	I	A	G	H	K	V	I	G	T	V	L	V	G	P	T
N	V	E	I	E	V	L	G	K	R	V	R	A	T	I	M	T	G	D	T
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	
P	V	N	I	I	G	R	N	L	L	T	Q	I	G	A	T	L	N	F	
P	V	N	V	I	G	R	D	T	M	T	Q	I	G	A	T	L	N	F	
P	I	N	I	F	G	R	N	I	L	T	A	L	G	M	S	L	N	L	

Here, we estimated the predicted change in activity in PR20 respect to both PR and Cam2. For that we compared spectral values for f=0.0584 ± 0.004 corresponding to PR20, PR and Cam2. Indeed, we used the same procedure as described in[5], and tried to predict possible increase/reduction in PR20 activity at the frequency f=0.0606, within the confidence interval for the theoretically optimal peak of f=0.0584 ± 0.004 reported in5.

We obtained that the peak at f=0.0606 is reduced in PR20 to 50% of the amplitude of PR. This could explain the lower catalytic activity reported for PR20 reported in[6].

In5, we picked as model wild protease the sequence

">sp|P24107|513-611 Human Immunodeficiency Virus (CAM2)",

As it can be seen from Table I, between Cam2 and PR there are notable differences.

Compared to Cam2, PR20 exhibits 49 mutations, meaning that almost half of aminoacids are mutated. Eleven of the PR20 mutations are shared by PR and Cam2 (see table I). Curiously, none of the 4 mutations respect to PR corresponding to the "catalytic first shell" is common to Cam2 and PR. This could explain the higher catalytic activity of PR respect to Cam2.

Surprisingly, comparison of peak amplitudes revealed that the spectral peak corresponding to PR20 is 3.83 times higher than the peak for Cam2.

It seems that these results corroborate, on one hand, the experimentally reported reduction in catalytic activity of PR20 when compared to PR[6], as well as the viability of PR20 when tested *in vivo*[7], which is here supported from the comparison of PR20 with the more "natural" sequence of Cam2. Again it is confirmed the capability of mutated versions of HIV protease to keep catalytic activity. In this case almost 50% of the aminoacids are changed respect to a wild type and catalytic activity is kept higher than some wild type proteases. This illustrates the huge adaptation capability inherent to HIV protease.

Our results point again to the applicability of the RRM for numerical predictions of different HIV protease mutants. This in our opinion might help optimizing the search of efficient HIV protease inhibitors.

REFERENCES

1.- Cosic I, Pirogova E, Qiang F. Electromagnetic Properties of Biomolecules. FME Transactions 2006; 34: 71-80

2.- Cosic I, Pirogova E. Bioactive Peptide Design using the Resonant Recognition Model, Nonlinear Biomedical Physics 2007; 1: 1-7.

3.- Ho MW. The real bioinformatics revolution - proteins and nucleic acids singing to one another?. Science in Society 2007; 33: 42-45.

4.- Cosic I, Nesic D. Prediction of 'hot spots' in SV40 enhancer and relation with experimental data. Eur J Biochem 1987; 170, pp: 247-252.

5.- Hernandez Caceres JL, Cosic I, Cosic D. Retroviral proteases viewed through the resonant recognition model, MD-Medical Data 2014; 6: 117-12.

6.- Johnson A, Shen CH, Aniana A, Sayer JM, Louis JM, Weber IT. HIV-1 protease with 20 mutations exhibits extreme resistance to clinical inhibitors through coordinated structural rearrangements. Biochemistry 2012; 51: 2819-2828.

7.- Louis JM, Aniana A, Weber IT, Sayer JM. Inhibition of autoprocessing of natural variants and multidrug resistant mutant precursors of HIV-1 protease by clinical inhibitors. Proc Natl Acad Sci USA 2011; 108: 9072-9077.

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