Computational Screening for Small Molecule Inhibitors of Talin/ β3 Integrin Tail Interactions

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Background

Talins are a family of cytoskeletal adaptor proteins involved in the activation of integrin cell adhesion molecules and serve a role in linking a cells cytoskeleton to the extracellular matrix. By binding the cytoplasmic tail of integrin beta chains, Talin induces conformational changes in integrins that result in increased integrin affinity for ligands. Talins nucleate focal adhesion signaling complexes to meditate interactions with F-actin and regulate focal adhesion turnover. The N-terminus of the talin head is composed of a FERM domain, which includes the F3 domain that is responsible for binding with integrin tails.

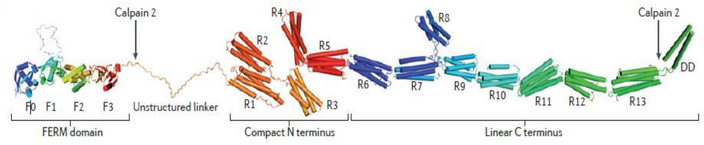


Figure 1: (Ref. 1) Structural representation of Talin.

Integrin and talin signaling is linked to pathological conditions including chronic inflammation and cardiovascular disease. As such, it may be beneficial to find drugs that block talin/integrin interactions. Here we identify candidate drugs that may bind to talin and potentially prevent interactions with integrin tails.

Methodology

Computational big data drug screening methodologies were implemented on the UH Opuntia cluster to dock 638,636 compounds as a subset of the ZINC database of drug-like leads. Autodock was deployed on hundreds of CPUs in parallel using in-house scripts to find molecules that might bind the talin F3 domain (PDB:2H7E) in the groove that associates with the beta tail of integrins. Compounds were screened and those with the most favorable binding energies were selected for further analysis.

	2H7E	3G9W
β integrin (organism)	*Mus muculus*	*Homo sapiens*
Talin (organism)	*Gallus gallus*	*Mus muculus*

Using VMD,PDB 2H7E was aligned with PDB 3G9W, which included the talin F3 domain in complex with the F2 domain.

The structure-function relationships were then evaluated in the docked complex.

Results

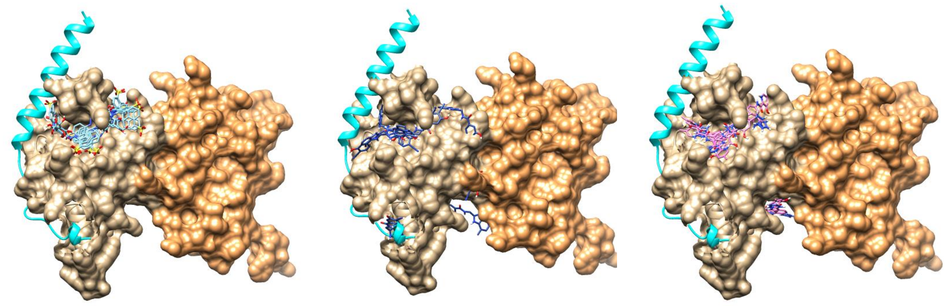
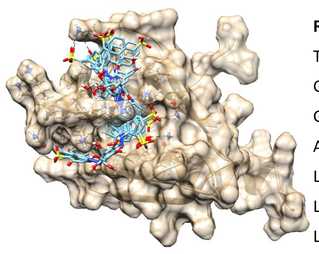


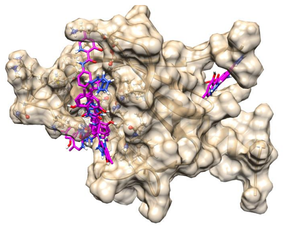
Figure 2: Talin F3 domain docked with FDA compound ZINC 03830332 (Left), DE compound ZINC000442682773(Center), and CD compound ZINC000494890529 (Right). Light blue helix is the Beta tail of integrin

Table 1: The top ten compounds from each drug database with the most favorable binding energies with the Talin F3 domain

FDA		DE		CD	
Compound	**Energy (kcal/mol)**	**Compound**	**Energy (kcal/mol)**	**Compound**	**Energy (kcal/mol)**
ZINC03830332	-8.9	ZINC000120038608	-8.2	ZINC000494890529	-8.0
ZINC08101077	-8.9	ZINC000442682773	-8.2	ZINC000357051337	-7.9
ZINC08101078	-8.6	ZINC000344447282	-8.1	ZINC000356060460	-7.8
ZINC08101079	-8.6	ZINC000195409314	-8.1	ZINC000356060460	-7.8
ZINC08101049	-8.5	ZINC000346684726	-8.0	ZINC000263411707	-7.7
ZINC08101050	-8.5	ZINC000348297419	-8.0	ZINC000348811417	-7.7
ZINC11681507	-8.4	ZINC000352098683	-8.0	ZINC000352110452	-7.7
ZINC03830554	-8.3	ZINC000353766898	-8.0	ZINC000355109177	-7.7
ZINC08101052	-8.3	ZINC000358365721	-8.0	ZINC000366818668	-7.7
ZINC03831187	-8.1	ZINC000141358705	-8.0	ZINC000368734590	-7.7



Residue	Distance (Å)
TYR378	3.67
GLN349	3.101
GLN374	3.237
ARG339	3.017
LYS318	3.583
LYS320	3.008
LYS343	3.12



Residue	Distance (Å)
TYR378	3.593
SER379	2.857
GLN374	4.03
ARG339	2.997
LYS318	4.617
ASP341	3.153
GLU317	3.234

Figure 3: Interactions between Talin and ZINC03830332 (right) , and ZINC000494890529 (left)

Thirty compounds were identified and selected for further analysis based on their binding energies, which ranged from approximately -7.7 kcal/mol to -8.9 kcal/mol. These energies are not as favorable as energies for good lead compounds generally are. However, these compounds serve as a good reference points as this computational screen is ongoing and new candidates will emerge. The majority of the identified compounds appeared to bind in the same groove of talin. Some residues from the interactions that may be involved in stabilizing the talin-drug complex were also identified.

Conclusions

- This project aimed to identify candidate drugs that might prevent interactions between talin and integrin tails. Several compounds were identified as potential inhibitors based on their binding energies and clusters. Although these compounds have mild binding energies, they serve as initial starting points for my continued screening of the ZINC database.
- The integrin tail aa's E726, F727, K729, F730, E733, R734, A737, and W739 are in the B3/Talin interface.

References

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