STEM SCHOLARS PROGRAM 2013

Homology Modeling of an Interleukin Involved in Cancer-Specific Apoptosis

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Abstract

Interleukin has emerged as a unique member of the IL-10 gene family, displaying a broad range of antitumor properties including cancer-specific induction of apoptosis, inhibition of tumor angiogenesis, and modulation of anti-tumor immune responses. Despite an improved understanding of interleukin biology, the underlying molecular mechanisms that allow Interleukin to induce cancer-specific apoptosis remains to be fully defined. To address this question, a homology model of Interleukin has been constructed, and receptor studies have been performed to broaden the understanding of Interleukin interactions. A reliable three-dimensional structure of human Interleukin was generated using YASARA program, based on known crystal structures of IL-20, IL-19, and IL-10. Applying validation programs revealed that the model has good quality. Furthermore, in this study we modeled three dimensional structure of Interleukin based on the high quality homology modeling approach to establish a basis for future researches about its biological function and interaction properties.

Introduction

Interleukin belongs to the IL-10 family of cytokines. This family includes IL-10, IL-19, IL-20, IL-22, Interleukin, and IL-26. Multiple studies have demonstrated that expression of Interleukin by an adenoviral expression system (Ad.Interleukin) induces growth suppression and apoptosis in a broad spectrum of human cancer cells, including those from melanoma, malignant glioma, fibrosarcoma, and carcinomas of the breast, cervix, colon, rectum, liver, lung, ovary and prostate, without exerting any deleterious effects on their normal counterparts. Little is known about the cytokine function of Interleukin other than its production in cells having immune functions in humans including melanocytes, stimulated monocytes and specific populations of T-lymphocytes, and its ability to stimulate proinflammatory cytokine production. The currently recognized Interleukin receptor complex consists of two sets of heterodimeric chains, IL-20R(R) and IL-20R2(B) or IL-22R1 and IL-20R2. The crystal structures of IL-20, IL-19, and IL-10, have been determined. Based on the information extracted from these 3D structures, as well as sequence alignments and secondary structure prediction, one can draw several conclusions about IL-10 family members' secondary, tertiary, and quaternary organization.

Experimental Design

1. Build Homology Model (YASARA)
2. Model Assessment (SAVes v.2)
3. Model Refinement (YASARA)
4. Model Assessment (SAVes v.2)
5. Molecular Dynamics Simulation with Receptors (YASARA)

Results

Template Selection:

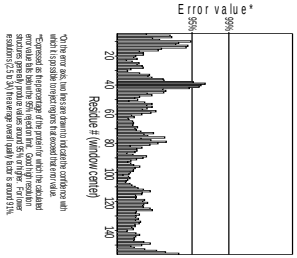
Template	Total Score	Align Score	Cover	ID	Resolution	Description
1	93.33	193.0	95%	4DOH	2.80 Å	IL-20
2	83.25	151.0	93%	1N1F	1.95 Å	IL-19
3	47.05	82.0	94%	2ILK	1.60 Å	IL-10
4	40.76	81.0	89%	1ILK	1.80 Å	IL-10
5	38.79	87.0	88%	1VLK	1.90 Å	Ad.IL-10

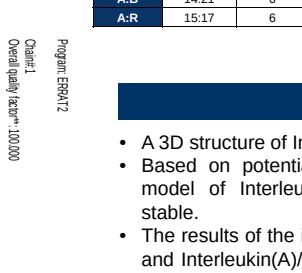
Results

Alignment Results:

Model Assessment and Model Refinement:

Model	Pro-check Errors	Verify 3D	ERRAT
Interleukin Initial	2	90.68% PASS	97.368
Interleukin EM	2	95.03% PASS	**100.000**
Interleukin MD	0	96.27% PASS	95.364
Interleukin EM->MD	0	91.30% PASS	98.675





Molecular Dynamics Simulation with Receptors Results:

Potential Energy

Interleukin Chains	Energy (kJ/mol)	IL-20 Chains	Energy (kJ/mol)
A+B+R	-23.43E+04	A+B+R	-23.81E+04
B+R	-15.19E+04	B+R	-15.39E+04
A	-7.390E+04	A	-7.464E+04

Electrostatic Energy

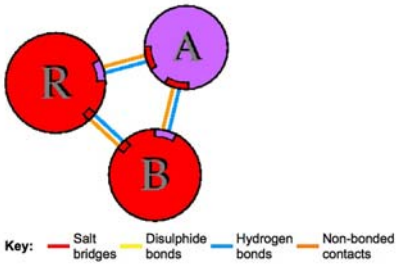
Interleukin Chains	Coulomb (kJ/mol)	VdW (kJ/mol)	(+)	IL-20 Chains	Coulomb (kJ/mol)	VdW (kJ/mol)	(+)
A+B+R	-24.47E+04	-4.202E+04	-28.67E+04	A+B+R	-24.46E+04	-4.142E+04	-28.60E+04
B+R	-17.13E+04	-2.847E+04	-19.98E+04	B+R	-17.27E+04	-2.861E+04	-20.13E+04
A	-7.187E+04	-1.221E+04	-8.408E+04	A	-6.968E+04	-1.139E+04	-8.107E+04

Interactions	Interleukin	IL-20
A+(AB+AR)i	-8.236E+04 (kJ/mol)	-8.415E+04 (kJ/mol)
(AB+AR)i	-8.457E+03 (kJ/mol)	-9.504E+03 (kJ/mol)
	-2.021E+03 (kcal/mol)	-2.272E+03 (kcal/mol)

Interactions	Interleukin	IL-20
A+(AB+AR)i	-8.699E+04 (kJ/mol)	-8.472E+04 (kJ/mol)
(AB+AR)i	-2.911E+03 (kJ/mol)	-3.657E+03 (kJ/mol)
	-695.78 (kcal/mol)	-874.02 (kcal/mol)

Interactions Results and Comparison:

Interactions	IL-20 - Interleukin
Potential	-250.30 (kcal/mol)
Electrostatic	-178.25 (kcal/mol)
Bond	-72.05 (kcal/mol)



Chains Interleukin	Interface Residues	Hydrogen Bonds	Non-Bonded Contacts
A:B	14:21	6	66
A:R	15:17	6	80

Chains IL-20	Interface Residues	Hydrogen Bonds	Non-Bonded Contacts
A:B	17:18	14	94
A:R	16:17	7	85

Conclusions

- A 3D structure of Interleukin was built using homology modeling.
- Based on potential energy differences we conclude that the model of Interleukin(A)/IL20R1(R)/IL-20R2(B) is energetically stable.
- The results of the interactions between Interleukin(A)/IL-20R1(R) and Interleukin(A)/IL-20R2(B) show that the model of Interleukin is interacting similarly to IL-20.
- Further analysis of the model is needed to validate stability.

References

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