Cancer Therapeutics — Harnessing Integrin Inhibition Property of Modified Naturally Secreted Peptide

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Targeted peptide cancer therapies which are less toxic compared to synthetic chemotherapies,is a research field of growing interest.Cell surface receptors Integrin-avß3(avß3),which recognizes RGD motifs of ligands,is upregulated in endothelial cells and tumor cells.Ligand Fibronectin(FN)interacts with avß3 via its RGD(Arg-Gly-Asp)motif,promoting angiogenesis and tumor cell invasiveness.avß3 has been explored as a therapeutic target for years,but there hasn't been any FDA approved avß3 antagonist.Cyclic Lasso peptides are promising anti-cancer peptides with low toxicity/drug resistance,high stability and resistance to proteases.This study evaluates interaction of peptide secreted by E.coli,MicrocinJ25(MccJ25)with avß3.MccJ25 variant with RGD motif (MccJ25v;sequence:GGAGHVPEYFVRGDTPISFYG)is selected.Docking between selected active sites of avß3 with MccJ25v and FN monomer with RGD was performed on softwares HADDOCK/PyRx.Binding energies and scores in interactions of avß3 and MccJ25v were superior to interactions with FN.Next,MccJ25v was evaluated for:allergenicity,toxicity,angiogenesis,IL-4 induction,anti-cancer ability,and hemolysis.MccJ25v showed undesired induction of IL-4 and less anti-angiogenesis.To eliminate undesired effects,mutations were done and a novel mutation in MccJ25v(GGGGHHPEDFVRGDFPISFCK)with no undesired effects was selected.Repeat docking with mutated MccJ25v and aVß3,resulted in best binding with aVß3 and involvement of majority of selected aVß3 active sites as well as additional sites in interaction.Drug likeness of MccJ25v with novel mutation is accpetable.MccJ25v with novel mutation can inhibit aVß3 function while competing with FN and can be developed as cancer therapy.Experimental evaluations are next steps to assay therapeutic effect of MccJ25v.

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