Recent Applications of Retro-Inverso Peptides

Subjects: Biochemistry & Molecular Biology

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Definition

Retro-inverso peptides possess reversed sequences and chirality compared to the parent molecules maintaining at the same time an identical array of side chains and in some cases similar structure. The inverted chirality renders them less prone to degradation by endogenous proteases conferring enhanced half-lives and an increased potential as new drugs. However, given their general incapability to adopt the 3D structure of the parent peptides their application should be careful evaluated and investigated case by case.

1. Topology, Structural Characteristics

As therapeutic agents, peptides have fascinating properties, such as very high specificity and binding affinity, generally low toxicity, and low risk of drug interactions [1]. Moreover, due to the high diversity which is sequence- and structure-dependent, they can be designed as potential drugs to target almost any disease. On the other hand, natural peptides, due to their low size and high sensitivity to most proteases, are quickly excreted or anyhow degraded, resulting in poor biodistribution, bioavailability, and rapid clearance [2], and thus limited therapeutic potential [2]. To increase peptide half-life, stability and bioavailability, many approaches have been proposed including PEGylation, backbone modifications, cyclization, side chain stapling, and lipidation [3][4]. Among these, modification of the backbone is one of the most invasive approaches, as it may profoundly affect the conformation of peptides, especially when it involves alteration of the residue's isomerization.

All amino acids (except glycine) possess chiral centers and occur in nature almost exclusively as L-enantiomers in proteins and natural peptides. D-amino acid-containing peptides are also found in nature, mainly in some frog species and bacteria, as a result of post-translational modifications [5].

The hydrogen bonds between the CO acceptors and NH donors generate a network of highly stabilizing interactions in peptides arranged as α-helices and β-sheets. If the network is removed, the stability of the 3D structure will be severely compromised in the retro-inverso mimetics, largely affecting their activity [6]. From a topological point of view, the RI analogues of larger peptides [7][8] could adopt conformations similar to that of the parent peptide when the full-length protein or part of it predominantly contains structural elements whose energy in the Ramachandran map is not drastically changed during the conversion like in β-sheets and γ-turns. In this case, they are likely to be stabilized by similar side-chain-to-side-chain interactions. This observation is consistent with results reported in literature [6][9][10][11]. As an example, Peggion and coworkers in 2009 [12] proposed a structure-function relationship study on a mimetic peptide of the Parathyroid hormone (PTH) spanning residues 1-11 (PTH(1-11)). This peptide is a ligand of the PTH type-I receptor and was studied through the synthesis and characterization of all-D PTH retro-inverso analogues. The retro-inverso RI-PTH(1-11) analogues showed a reduced biological activity compared to the parent peptide, because of the absence of the α-helical structure which could be induced by introducing an Aib residues on the N-terminal position [13].

The main advantages of retro-inverso peptides as potential biotherapeutics are the improved stability in vitro and in vivo and the novelty in terms of intellectual property as compared to the parent peptides. The interest around this subclass of molecules is driven by their potential use in a vast area of applications here reviewed, including diagnostics, cancer therapeutics, neurodegenerative diseases, and new antibiotics (as antimicrobial peptides). Some potential applications are here reported.

2. Anticancer Applications—Diagnostic

An example of the use of RI analogues is provided by Calvanese et al. [14] who designed a series of cyclic peptides embedding the retro-inverso (RI) version of the consensus sequences RPL/LPPR, corresponding to peptides capable of preventing VEGF binding to VEGFR1 [15] and VEGFR2 [16], and to specifically inhibit human endothelial cells (EC) proliferation in vitro [16]. Direct binding experiments of the peptides to VEGFR1 and VEGFR2 identified a peptide that bound both receptors with a K D in the low micromolar range but with a significant selectivity for VEGFR1 respect to VEGFR2 thus showing a potential as VEGFR1-selective diagnostic probe.

Other examples are reported below.

The peptide VAP (**Table 1**) was shown to have high binding affinity in vitro to GRP78 protein, which is overexpressed in gliomas, glioma stem cells, vasculogenic mimicry, and neovasculature [17]. The prediction of binding for the analogue RI-VAP to GRP78 was similar to that of the parent peptide and, in addition, remarkable tumor accumulation was observed experimentally by imaging in vivo. RI-VAP-modified paclitaxel-loaded polymeric micelles had better anti-tumor efficacy compared to free taxol, to paclitaxel-loaded simple micelles, and to micelles modified with parent peptide.

Table 1. Names, peptide sequences reported in the review and their applications.

Name	Sequence [1]	Application	Ref
Anticancer Applications—Diagnostic			
VEGF-P3(CYC)	$I^{76}TMQ^{79}CG^{92}IHQGQHPKIRMI^{80}CE^{93}MSF^{96}$ *	Inhibition angiogenesis	[18][19]
$_D$(LPR)	$_D$(Leu-Pro-Arg)	Inhibition retinal angiogenesis; Diagnostic	[15][14][20]
SP5	PRPSPKMGVSVS *	Drug delivery	[21][22]
$uPAR_{88-92}$	SRSRY *	Maintaining chemotactic activity and triggers directed cell migration and angiogenesis	[23][24]
RI-3	Ac-$_D$(Tyr- Arg-Aib-Arg)- NH_2	Prevent extracellular invasion by tumor cells	[25]
$_D$(RGD)	$_D$(Asp-Gly-Arg)	Diagnostic	[26][27][28]
VS	SWFSRHRYSPFAVS *	Glioblastoma multiforme (GBM)	[29][30]
VAP	SNTRVAP *	Gliomas, glioma stem cells, vasculogenic mimicry and neovasculature	[17]
WSW	SYPGWSW *	Glioma cells and tumor neovasculature	[31]
BK	RPPGFSPFR *	Glioma cells	[32]
FP21	YTRDLVYGDPARPGIQGTGTF *	Ovarian cancer	[33][34][35]
T7	HAIYPRH *	Drug delivery	[36]
Applications in Immunology			
TG19320	$(rty)_4K_2KG$	IgG binding	[37][38]
VSVp	RGYVYQGL *	antigen surface of hepatitis B virus	[39]
OVAp	SIINFEKL *	antigen surface of hepatitis B virus	[39]
PS1	HQLDPAFGANSTNPD *	antigen surface of hepatitis B virus	[39]
HAI	HAIYPRH *	Crossing BBB	[40]

Name	Sequence	Application	Ref
THR	THRPPMWSPVWP *	Crossing BBB	[40]
InsB:9–23	HLVEALYLVCGERGG *	Analogue of diabetogenic islet peptide—prevents T-cell activation in humanized model mice	[41][42]
Application in Neurodegenerative Diseases			
Amytrap	WKGEWTGR *	Blocking the oligomerization and aggregation of $A\beta_{1-42}$	[43][44][45][46][47]
$IAPP_{11-20}$	RLANFLVHSS *	Strong inhibitory effects on amylin aggregation in T2DM	[48]
β-syn_{36-45}	GVLYVGSKT *	Reduction of amyloid fibril and oligomer formation	[49]
Application in Antimicrobial Antibiotics			
RI1018	rrwirvavilrv	Preventing formation of Biofilm	[50]
RI-JK6	rivwvrirrwqv	Preventing formation of Biofilm	[50]
RI-73	lwGvwrrvidwlr	Damaging the bacterial membrane	[51]
BMAP-28	GGLRSLGRKILRAWKKYGPIIVPIIRIG *	Broad antimicrobial activities	[52]

[1] The sequences reported are those of the parent peptides * (L-residues), unless otherwise indicated, like reporting D residues as lower-case letters or adding a “D” before the sequence.

Follicle-stimulating hormone receptor (FSHR) expression is limited to the reproductive system [53][54] and might be targeted to deliver drugs against ovarian cancer with high selectivity and specificity. In particular, nanoparticles carrying the RI variant of the peptide FP21 showed to bind FSHR (**Table 1**). They were thus used as an ovarian cancer targeted delivery system [33][34][35], showing improved biostability compared to the parent peptide, with no degradation even after 12 h incubation with proteolytic enzymes. The data obtained on the RI peptide encouraged further developments and optimizations of the molecule for treating ovarian cancers expressing FSHR [33].

3. Conclusions and Future Perspectives

In the field of peptidomimetics, retro-inversion has been largely explored to improve peptide stability while retaining the parent molecule’s activity. Changing the order of the amino acids and their configuration has been also a mean of introducing novelty and to overcome existing intellectual property claims [55]. The first examples of their use were reported by M. Goodman in the mid-1970s [56], who was interested in the study of stereochemical and conformational properties of retro–inverso (RI) amide bonds in linear peptides. Interesting examples were next reported by Merrifield with studies on the CAMEL peptide [57][58], which was a chimeric peptide derived from the merging of two AMP. Despite the amazing results reported in literature, the application of retro-inversion to generate peptidomimetics is still rare or however uncommon.

Beyond these basic rules applicable to short peptides or other specific examples, the reasons for the frequent failure of RI isomerization of longer molecules are still largely unclear, and definite instructions for possibly improving the success rate are unresolved. The reversal of the peptide backbone and the shift of the H-bond network it is involved into is a major alteration of the fine equilibrium of the forces that supports the conformation of a peptide having an organized 3D structure. Therefore, as for the folding of a natural molecule, the lack of one such important puzzle piece prevents the correct assembling of the structure although the side chains may potentially have access to the same conformational space of the parent molecule. We can thus conclude that the design of a successful retro-inverso analogue of a folded peptide has the same complications as for the de novo design of a new

protein or peptide and one should thus proceed following the rules, still not well understood and codified, of protein folding, exploiting and using the geometrical and structural features of amino acids in D configuration. For example, the RI isomerization and structure reconstruction of the MDM2/MDMX peptide inhibitor stingin, which adopts an N-terminal loop and a C-terminal α-helix, lead to an isomer that partially retained binding (3.0–3.4 kcal/mol reduction) and showed a decreased ability to prevent the interaction with p53 [59]. These conformation and energy issues have been often discouraging because of the frequent loss of biological activity observed in larger molecules showing well-defined tridimensional organizations. Merrifield indeed soon observed that the efficiency of peptide retro-inversion was not only related to inversion of its chirality but to the global change of the 3D conformation [57]. These observations have been indirectly confirmed showing that retro-inverso analogues of unstructured peptides more often maintain or even increase the activity compared to the parent peptide [60].

On the other hands, peptides that assemble into β-sheets adopting extended conformations establish a large and well-organized network of interactions, mostly H-bonds, with the adjacent molecules. Also, the side chains are well packed each other. In this case, despite the strong backbone interactions, retro-inverso analogues have more chance to be successful if the registry of H-bonds and of side chain-to-side chain interactions is corrected to account for the inverted amide bonds. The molecular dynamic simulations of amyloid fibrils in AD [61] or amylin in T2D [62] indeed showed that the interactions of both side chains and backbone of RI peptides were re-aligned establishing different patterns of contacts and hydrogen bonding. Also, the twist of the RI analogue β-sheets was similar and the complex had only slightly lower stability compared to the parent peptides.

Computational approaches might be of great help and might open a new season in this field as suggested by Robson [63]. Despite their many limitations, we believe their use still has a place in the design of drugs based on bioactive peptides. This belief stems from the simplicity of the design, from the rapidity in making synthetic peptides and from the immediate benefits resulting when the molecules maintain their activity. Therefore, this review would be an incentive to continue working with these types of molecules, also to further investigate the conformational and topological space they need to occupy to fully mimic bioactive peptides with complex structure.

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Keywords

retro-inverso peptides;anticancer peptides;drug delivery;peptide antigens;Aβ;IAPP;antimicrobial peptides