A chirality change in XPC- and Sfi1-derived peptides affects their affinity for centrin

Centrins are small Ca^{2+}-binding proteins that bind several cellular targets: XPC, Sfi1, Sac3, and transducin β. Thus, centrins are involved in several cellular processes, including centrosome division (Sfi1 protein), DNA repair (the recognition of UV-induced damage by XPC protein), mRNA export (Sac3 protein) and transduction (transducin β protein) that are regulated by calcium.

Centrins bind targets through the hydrophobic triad Tryptophane-x-x-Leucine-x-x-x-Leucine. However, the sequence of this motif is in the reversed amino-acid sequence Leucine-x-x-x-Leucine-x-x-Tryptophane in centrin's other targets (Sfi1, Sac3 and transducin β). Structures of centrins in complex with truncated targets or target-derived peptides (i.e., XPC, Sfi1, or Sac3) have been solved. In all cases the Phenylalanine113 residue of human centrin is the main residue involved in target binding.

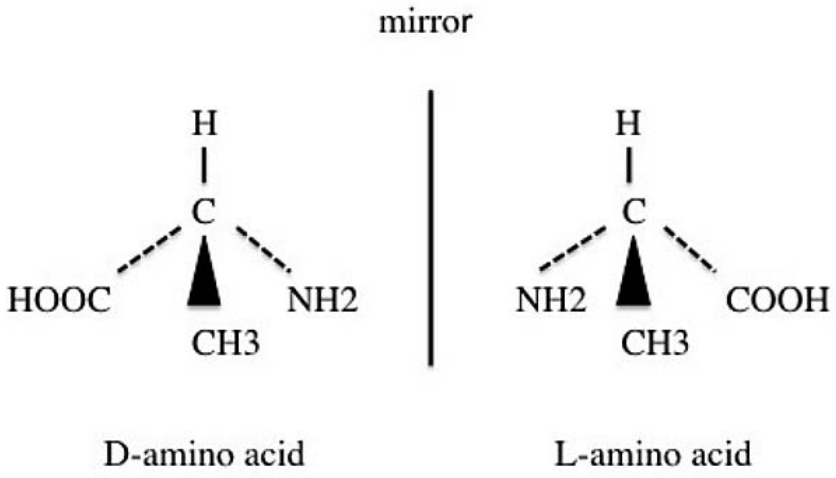

Fig. 1. L- and D-amino acids are mirror images.

Homochirality is a rule of living cells. Thus, proteins are composed of L-amino acids, whereas RNA and DNA are composed of D-sugars. However, D-amino acids (Fig. 1) exist in vivo and serve as a component of bacterial cell walls. In eukaryotes, D-amino acids have been found in various tissues, including cartilage, hair, and tooth enamel. In these examples, amino acid racemization is age-dependent. However, racemization can also be functional, as in the case of the age-dependent aspartate racemization of mammalian histone H2B. Amino acids racemization occurs also in reverse; indeed, bacteria use external D-amino acids as a source of nitrogen via enzymatic racemization.

D-peptides have been used successfully in many applications. Indeed, D-peptides have been used for the treatment of Alzheimer's disease in mice [Funke et al 2010]. These successes have encouraged us to analyze the binding of D-peptides to centrin. We analyzed the affinity of human centrins 1 and 2 for several target-derived peptides composed of either L-residues or D-residues.

The change in chirality from L-residues to D-residues led to a reduction of centrin binding to XPC-derived peptide and abolished the binding to Sfi1-derived peptide. The chirality change affected the behavior of the centrin target in the same way regardless of its sequence orientation. However, this effect seemed to be more important for Sfi1; therefore, this extent of the inhibitory effect of chirality change was dependent on orientation.

The difference observed between the L- and D- isomers was most likely due to the chirality change, which likely reoriented the residues of the target-derived peptide. D-isomers are the mirror image of L-isomers, and consequently, the difference in conformation observed between the L-targets of reverse sequence also exists for their respective D-isomers.

Our experiments were designed from the perspective that the target-derived peptides could be used in vivo to block the binding of centrin to its cellular targets and to block cellular mechanisms that require centrin function.

We propose that XPC-derived D-peptides could be used to target centrin in vivo. However, further investigation of peptide sequence is needed to increase the affinity of the XPC-derived D-peptide for centrin. The main advantage of using D-residues lies in their resistance to proteolysis, but future investigation is required before their use in vivo, including studies of cell targeting, cell penetration of D-peptides and consequences of D-peptide penetration in the cell.

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