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Determinants of the membrane orientation of a calcium signaling enzyme CD38.

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Recommendations:

Very Good **14 Apr 2015**

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INTERESTING HYPOTHESIS

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I found this article interesting because it suggests a solution to the topological paradox of how CD38 enzymatically synthesises cyclic ADP-ribose (cADPR). cADPR is a secondary intracellular messenger molecule that is synthesised in response to extracellular stimuli and mobilises calcium (Ca2+) from organelle stores {1}. A novel enzyme from the mollusc Aplysia californica, named ADP-ribosyl cyclase, was shown to synthesis cADPR from NAD2. Additionally, this enzyme has been shown to synthesise another secondary Ca2+ messenger, nicotinic acid adenine dinucleotide phosphate (NAADP) from NADP {3}. The mammalian homologue of this is the membrane protein cluster of differentiation 38 (CD38) {4}, which also has these enzymatic activities but has a topological paradox, as it is in a type II membrane orientation with the catalytic domain in its extracellular region {5}. It has been proposed that a subset of the protein may natively exist in a type III conformation with the enzymatic domain facing the cytosol {6}.

The authors showed that as per the 'positive-inside rule', mutations either altering the positive residues of the internal N-terminal domain, or those that mimicked its phosphorylation resulted in an inversion of the peptide into a type III conformation and increased cADPR production. This was tested using a novel antibody for the C-terminal domain of CD38 when it is un-glycosylated. Additionally, mutations that further stabilised the type II orientation reduced the production of cADPR. This work supports a previous report that shows that some CD38 exists in a type III orientation in HL-60 cells and both primary and immortal monocytes {7}. However, there still remains uncertainty as to how the enzyme can natively synthesise NAADP, which requires an acidic environment {3}.

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Disclosures
None declared

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Abstract:

ABSTRACT

CD38 catalyzes the synthesis of two structurally distinct messengers for Ca(2+)-mobilization, cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP), from cytosolic substrates, NAD and NADP, respectively. CD38 is generally thought of as a type II membrane protein with its catalytic site facing outside. We recently showed that CD38 exists, instead, in two opposite membrane orientations. The determinant for the membrane topology is unknown. Here, specific antibodies against type III CD38 were designed and produced.
We show that mutating the positively charged residues in the N-terminal tail of CD38 converted its orientation to type III, with the catalytic domain facing the cytosol and it was fully active in producing intracellular cADPR. Changing the serine residues to aspartate, which is functionally equivalent to phosphorylation, had a similar effect. The mutated CD38 was expressed intracellularly and was un-glycosylated. The membrane topology could also be modulated by changing the highly conserved di-cysteine. The results indicate that the net charge of the N-terminal segment is important in determining the membrane topology of CD38 and that the type III orientation can be a functional form of CD38 for Ca(2+)-signaling.
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