Identification of SH2D3C as a Novel Interactor of DPP III

Sanja Tomić, Ana Tomašić Paić, Lucija Horvat and Mihaela Matovina

Sanja.tomic@irb.hr

Institute Ruđer Bošković, Bijenička 54, 10000 Zagreb, Croatia

The zinc dependent exopeptidase DPP III has broad specificity towards naturally occuring peptides four to eight amino acid residues long. In addition to its enzymatic activity DPP III interacts with other proteins and, through these interactions, participates in several pathophysiological processes in humans. One such 'moonlighting' activitiy of DPP III is mediated through its interaction with SH2D3C, one of three members of a protein family known as novel SH2-containing proteins (NSPs), which are characterized by the presence of both an SH2 domain and a Ras GEF-like domain (a domain similar to guanine nucleotide exchange factor domains of Ras family GTPases).

We have shown that SH2D3C binds to DPP III through its C-terminal Ras GEF-like domain using several low-throughput experimental methods, detected the colocalization of the proteins in living cells, and confirmed their direct interaction in the cytosol and membrane ruffles [1]. Computational analysis further supported the binding of the C-terminal domain of SH2D3C to DPP III. This was the first indication that SH2D3C might be an interactor of DPP III, and that their interaction might represent a link between the regulation of the oxidative stress response via the KEAP1–NRF2 pathway and the processes in which SH2D3C is involved, including cell adhesion, migration, and growth. Furthermore, we computationally mutated three Arg residues, Arg125, Arg159 and Arg598, of DPP III that form strong interactions with SH2D3C and whose mutations were detected in cancer cells, and studied the interaction of mutated variants of DPP III with SH2D3C.

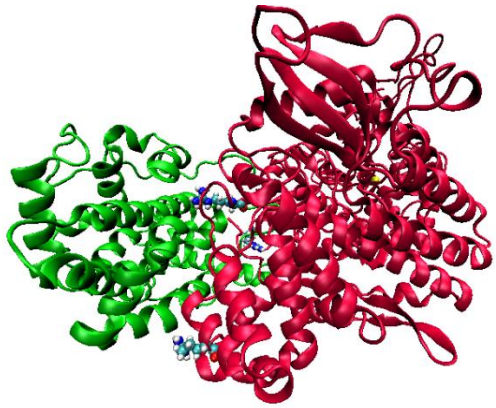

Figure 1. The DPP III - SH2D3C complex used in the computational study. Arginines that have been found to be mutated in cancer cells are shown in ball and stick representation.

Reference:

[1] M. Matovina, A. Tomašić Paić, S. Tomić, H. Brkić, L. Horvat, L. Barbarić, V. Filić, M. Pinterić, S. Jurić, A. Kussayeva, *Int. J. Mol. Sci.* **16** (2023) 14178.