Report for Experiment mx-1826: Structural Biology of the SMN complex

Scientific background :

Spliceosomal U-rich small ribonucleoprotein particles (U snRNPs) are the major building blocks of the pre-mRNA processing spliceosome [1]. Even though these particles can form spontaneously *in vitro*, their assembly *in vivo* requires a plethora of trans-acting assembly factors united in SMN- and PRMT5-complexes. The assembly pathway of U snRNPs can be divided into two distinct temporal phases. The early phase is dominated by the assembly chaperone pICln. pICln binds newly-synthesized Sm proteins and delivers them in a pICln-bound form to the PRMT5 complex, which consists of PRMT5 and WD45 (also referred to as MEP50) [2, 3]. The early assembly phase then segregates into two lines. In one assembly line, a stable hexameric ring intermediate is formed, which is composed of pICln and the Sm proteins D1, D2, F, E and G. Within this intermediate these Sm proteins are already pre-organizes into spatial positions adopted in the assembled U snRNP [1, 4, 5]. The other assembly line consists of pICln-D3/B, which may likely not dissociate from the PRMT5 complex. As a consequence of their association with pICln, Sm proteins are kinetically trapped and fail to proceed in the assembly pathway. The late phase of snRNP formation is dominated by the SMN complex (containing SMN and the Gemins 2, 6, 7 and 8 in *S. pombe*), which resolves this kinetic trap by dissociating pICln from the pre-organized Sm proteins and subsequently catalyzes the joining of Sm proteins with snRNA [1, 5, 6].

Results:

With data collected during this session, we were able to solve the 2.0 Å crystal structure of a minimal version of the *S. pombe* SMN (Yab8) protein (Fig. 1). Strikingly, the crystal structure reveals that, apart from the previously known oligomerization interface [7] in the YG box region, a second one exists which

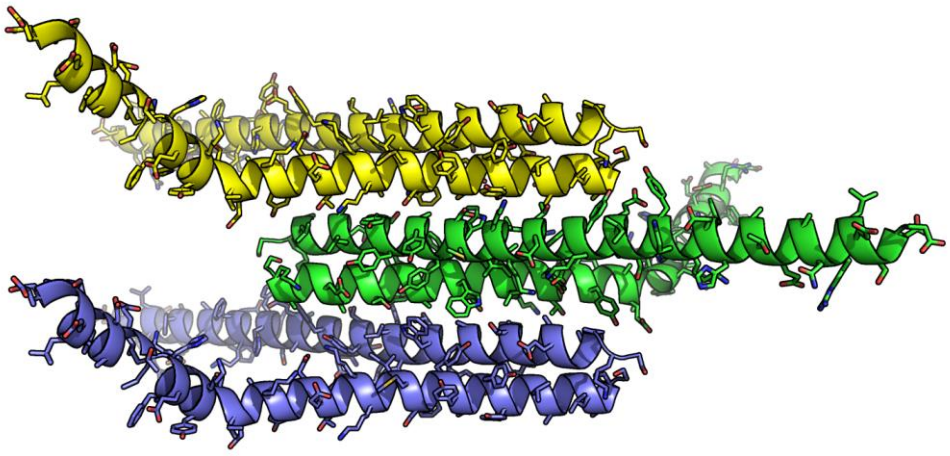

Fig. 1: Crystal structure of a minimal version of the *S. pombe* SMN (Yab8) protein (Three asymmetric units shown in different colors). The YG box motif facilitates a dimer contact, three dimers are shown in yellow, green and purple, respectively. A second interface forms a crystal contact (between differently colored entities) and may lead to the formation of higher order oligomers in solution.

explains the formation of high-molecular weight entities of the SMN complex.

A second crystal structure solved during this session is that of a complex between Gemins 6 and 7 and an interacting domain of Gemin 8. The 1.5 Å structure reveals that the interacting domain features a helix-turn-helix motif (Fig. 2). Taken together, both structures illustrate the mode of interaction of several key components of the SMN complex.

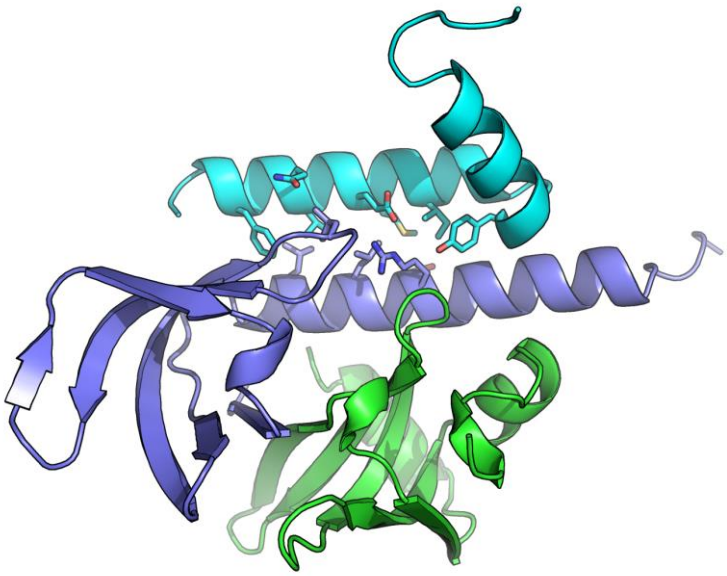

Fig. 2: Crystal structure of a complex between Gemins 6 (green) and 7 (purple) and an interacting domain of Gemin 8 (turquoise) solved at 1.5 Å.

In addition, we were able to collect a 3.5 Å dataset from a crystal of a complex between pICln and the PRMT5 TIM domain. The crystal structure of this complex would explain how the SMN complex interfaces with the PRMT5 complex to hand over SM proteins. While the dataset appears twinned, we were able to get a promising molecular replacement solution with a TIM model. We are currently working on the improvement and detwinning of these crystals.

References

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