1A3b

Redox-sensitive structural change in the A-domain of HMGB1 and its implication for the binding to cisplatin modified DNA

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High Mobility Group Box 1 (HMGB1) is a redox-sensitive protein that functions in both intra- and extra-cellular environments [1]. Inside the cell, it acts as a DNA chaperone, whilst outside of the cell it functions as an extracellular signal molecular. Two cysteines, in the A domain, C23 and C45, are in spatial proximity to make an intramolecular disulfide bond under oxidative conditions. The disulfide bond formation changes the HMGB1 functions. The oxidized HMGB1 has decreased binding affinity to cisplatinated DNA relative to the reduced form. However, the molecular reason for the reduced binding of the oxidized HMGB1 has remained unclear. That prompted us to solve the oxidized A domain structure, to see why the disulfide bonding in the A domain causes impaired affinity to cisplatinated DNA.

We successfully solved the oxidized A domain structure. The structural comparison between the oxidized and reduced A domains demonstrated that the oxidized form has the Phe38 ring flipped from that in the reduced form: Phe38 is the key residue in the binding to cisplatinated DNA (Fig. 1A) [3]. The model complex using the oxidized A domain structure showed the disorientation of Phe38 in the oxidized form may disable its intercalation to platinated-GpG lesion (Fig. 1B), which could explain the reduced affinity of the oxidized HMGB1 to the cisplatinated DNA [4].

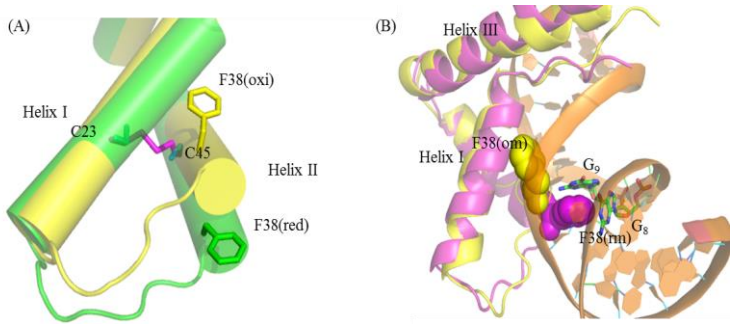

Fig.1. (A) The close up view of the parts comparing of helices I and II with inter helix linker in the reduced and oxidized A domains. (B) Comparing the model complexe with the crystal structure comprising of the reduced A domain and cisplatinated DNA.

[1] Tang D et al., Antioxid Redox Signal, 14, 1315-1335 (2011).

[2] Park S et al., Biochemistry, 50, 2567-2574 (2011).

[3] Ohndorf U.M et al., Nature, 399, 708-712 (1999).

[4] Wang J et al., BBRC, in press (2013).