# Protein phosphatase PP1-NIPP1 limits the DNA-repair capacity

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Abstract

PP1 is a member of the PPP superfamily of protein Ser/Thr phosphatases. It is a ubiquitously expressed enzyme that catalyzes over half of all protein dephosphorylation events in eukaryotic cells. In mammals PP1 interacts with over 200 PP1-interacting proteins (PIPs) that determine when and where the phosphatase acts. One of these PIPs is NIPP1, for nuclear inhibitor of PP1. To study the *in vivo* function of NIPP1 we have generated NIPP1 knockout models. A total NIPP1 knockout in mice is early embryonic lethal. However, the conditional knockout of NIPP1 in liver epithelial cells or skin keratinocytes has no major spontaneous phenotype, except for a moderate expansion of the stem-cell compartment. Strikingly, such NIPP1-deprived cells display a strongly enhanced DNA-repair capacity and a nearly complete resistance to mutagen-induced carcinogenesis. Conversely, the expression of a PP1-NIPP1 fusion in HeLa cells causes replication stress, as illustrated by the appearance of slow and stalled replication forks, and the accumulation of double-strand DNA breaks. Importantly, replication stress was not observed after the expression of PP1-NIPP1 fusions with mutated substrate-binding or PP1-anchoring domains of NIPP1. This strongly suggests that replication stress induced by PP1-NIPP1 stems from the dephosphorylation of FHA ligands by associated PP1. We are currently identifying the relevant substrates. Thus, our data indicate that PP1-NIPP1 limits the DNA-repair capacity.