The specialized DNA polymerase Kappa required to stabilize the checkpoint kinase Chk1

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¹Equivalent contribution

The replication of the genome is constantly challenged due to endogenous or exogenous fork barriers leading to replication fork stalling which is a cause of replicative stress. When stalled forks fail to restart, it can give rise to DNA breakage or chromosomal rearrangements. To prevent this genetic instability, the fork blockage is signalled by a set of proteins during the S phase through the ATR/Chk1 pathway [1]. In most of cancer cells, intrinsic disorder or chemotherapeutic treatments induce high level of replicative stress, making malignant cells dependent on the ATR/CHK1 signalling. Thus, targeting this pathway is appearing as a strategy to kill cancer cells.

Among the network of protein required to activate the ATR/Chk1 pathway, we previously demonstrated an unsuspected function of the most conserved specialized DNA polymerase: the DNA polymerase Kappa [2]. Indeed, we demonstrated that Pol Kappa is required to get the full phosphorylation of Chk1 in response to replicative stress in Xenopus extracts and in mammalian cells [3].

We now provide new data showing that in addition to its role at the stalled forks [3], Pol kappa is also involved to maintain the pool of Chk1. We observe that the depletion of Pol Kappa induces a Chk1 protein level decrease in mice and mammalian cells. The impact of Pol Kappa on Chk1 level is more obvious in the nuclear compartment than in cytoplasm and does not depend on exogenous replicative stress as it is observed in untreated cells. By different approaches, we show that Pol kappa and Chk1 belong to the same complex. In parallel, we identify that Pol Kappa interacts with USP7 (Ubiquitin Specific Protease 7), a deubiquitinase yet known to regulate Chk1 [4]. USP7 appears as a novel regulator of Pol Kappa since we show that the protein level of Pol Kappa depend on the catalytic activity of this deubiquitinase enzyme.

From our previous publication [3] and from literature [5], it is known that the level of Pol Kappa and Chk1 have to be maintain to prevent genome instability. Here, we provide preliminary data carried out by DNA spreading and showing defects in the forks restart after HU treatment (Hydroxyurea) when Pol Kappa or Chk1 are depleted by RNA interference. The expression of ectopic Chk1 can rescued the fork restart in both cases arguing that Pol Kappa and Chk1 work in the same pathway.

Taken together, this findings lead us to propose a model in which Pol Kappa, regulated by USP7, maintains a reservoir of Chk1 in the nucleoplasm making cells ready to answer to stress induced by the replication forks barriers.


