Genome instability is a salient feature of carcinogenesis. In eukaryotes, a genome maintenance machinery has evolved to deal with the threat of DNA damage, and multiple pathways have emerged to repair a wide-range of lesions. Ubiquitylation is a key post-translational modification that is prevalent around DNA damage sites and that regulates the stability and interactions of several repair proteins. Multiple Ubiquitin ligases, such as BRCA1, RNF8, RNF168, TRIP12 and the Fanconi core complex have emerged as key regulators of the DNA damage response and their mutations result in hereditary diseases and cancer formation. There is much less known about which deubiquitylases (Dubs) are involved in DNA repair. In this application, we describe a new function of a Dub (USP20) in mediating Chk1 phosphorylation after DNA damage by stabilizing Rad17. We define the functional and physical interactions between USP20 and Rad17 and we show that USP20 protects Rad17 from proteasome-mediated degradation by deubiquitylation. We also implicate USP20 in the resistance to DNA damaging agents and in the repair of DNA double strand breaks by homologous recombination. Finally, we reveal a functional interaction between USP20 and the MDM2-TP53 pathway, which is an important cancer therapy target.