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Autore	H. Christian Reinhardt
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Sommario/riassunto	For this eBook, and the associated Research Topic in Frontiers in Genetics, entitled: ‘Cancer-associated defects in the DNA damage response: drivers for malignant transformation and potential therapeutic targets’ we have selected 10 papers that each discusses important, yet distinct aspects of the response to DNA damage in normal cells and cancer cells. Using an evolutionary conserved signaling network called the ‘DNA damage response (DDR)’ cells maintain the integrity of their genome, and thus safeguard cellular functioning and the ability to create viably progeny. Initially, the DDR appeared to consist of few linear kinase-driven pathways. However, research over the past decades in model organisms, as well as in the human system has revealed that the DDR is a complex signaling network, wired by multiple parallel pathways and displaying extensive crosstalk. Besides phosphorylation, multiple other post-translational modifications, including ubiquitination and sumoylation, are involved to achieve chromatin remodeling and initiation of DNA repair. Also, rather than being a cell-intrinsic phenomenon, we increasingly appreciate that cell-cell communication is involved. The recognition and repair of DNA damage is essential to maintain normal physiology. Multiple pathological conditions have been attributed to defective DNA repair, most notably accelerated aging, neurodegeneration and cancer. In the context of cancer, through repair of DNA damage or elimination of irreparably damaged cells, the DDR clearly has a tumor-suppressive

role. Indeed, many tumor cells show partially inactivated DDR signaling, which allows proliferation in the context of DNA damage-inducing oncogenes. Simultaneously, loss of specific DDR signaling nodes creates a specific dependence of tumor cells on their remaining DDR components, and thus creates therapeutic opportunities. Especially in the context of cancer treatment, numerous targeted agents are under investigation, either to potentiate the cytotoxic effects of chemo-radiotherapy, or to induce synthetic lethality with cancer-specific alterations, with the treatment of BRCA1/2 mutant cancers with PARP1 inhibitors as a prototype example. We have selected four review articles that provide insight into the key components and the wiring of the DDR and DNA repair. Torgovnick and Schumacher review the involvement of DNA repair in the initiation and treatment of cancer, Brinkmann et al., describe the involvement of ubiquitination in DNA damage signaling and Jaiswal and Lindqvist discuss how cell-extrinsic signaling participates in communication of DNA damage to neighboring cells. In addition, Shatneyeva and colleagues review the connection between the cellular response to DNA damage and escape from immune surveillance. Concerning the therapeutic application of targeting the DDR and DNA repair, three articles were included. Krajewska and van Vugt review the wiring of homologous recombination and how this offers therapeutic opportunities. Additionally, Knittel and colleagues describe how genetic loss of the central DDR component ATM in chronic lymphocytic leukemia can be exploited therapeutically by targeting certain parallel DNA repair pathways. Syljuasen and colleagues report on how targeting of the DDR can be used as a therapeutic strategy in lung cancer. Finally, three chapters describe newly identified regulators of the cellular response to DNA damage. Von Morgen et al. describe the R2TP complex, Lezzi and Fanciluuli review the involvement of Che-1/AATF in the DDR, and Ohms and co-authors describe how retrotransposons are at the basis of increased genomic instability. Altogether, these articles describe how defective responses to DNA damage underlie disease - and especially in the context of cancer -can be exploited to better treat disease.