ID 07.6

Senescence and cell death triggered by the DNA alkylation damage O6-methylguanine

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Alkylating agents are potent mutagens and carcinogens. They are also cytotoxic, which is harnessed in cancer chemotherapy. In glioblastoma therapy, the 1st line drug is temozolomide (TMZ), which induces various DNA lesions including O6-methylguanine (O6MeG). If not repaired, O6MeG gives rise to DSBs due to futile mismatch repair (MMR) cycles, which finally trigger ATR/ATM activation and the DNA damage response (DDR). This leads to activation of apoptotic and the senescence pathways. We have shown that apoptosis and senescence follow the same kinetics, but different dose-responses. Thus, 8 d after treatment senescence reached a 3-fold higher level than apoptosis, indicating senescence is a main trait. Analysis of TMZ-induced senescent cells show high levels of trimethylated H3K9 and H3K27, both marker for senescence, high amounts of DNA double-strand breaks, which were located outside of telomers, and a sustained activation of the DDR. Although TMZ-induced DSBs persist in senescent cells, radiation-induced DSBs are still repaired. To further elucidate the role of O6MeG in apoptosis and senescence induction following TMZ treatment, we used a tet-on system to induce MGMT at defined stages after TMZ treatment and in senescent cells. Upregulation of MGMT immediately after TMZ treatment caused complete abrogation of apoptosis and senescence, while MGMT upregulation >3d following TMZ treatment had no impact on apoptosis and senescence induction. Upregulation of MGMT in senescent cells showed neither reduction of senescence nor induction of apoptosis in the senescent population. Senescent cells were also found in post-treatment cancer specimens. Overall, the data show that O6MeG-triggered senescence is a main response following TMZ treatment of glioblastoma cells and that O6MeG is required for induction, but not for maintenance of the senescent state. The amount of O6MeG required for triggering apoptosis and CSEN was determined. A search for senolytic drugs revealed some natural compounds of promising activity. The role of senolytics in cancer therapy will be discussed. Supported by DFG KA724/31-1.