Aberrant DNA damage response and receptor tyrosine kinase signaling in non-small cell lung cancer tumor initiating cells

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Aim
- Non-small cell lung cancer (NSCLC) is characterized by a chemo- and radiotherapy refractory phenotype.
- Here we aimed to elucidate if chemo- and radiotherapy resistance in NSCLC is attributed to a TICs phenotype and delineate components involved.

Results and conclusions
- CD133-positive NSCLC cancer stem cells or tumor initiating cells (TICs) showed increased survival and reduced apoptotic response after irradiation (IR) and cisplatin compared to bulk cells.
- A cisplatin-refractory phenotype of TICs was confirmed in vivo in a mouse xenograft model.
- TICs displayed less pronounced G2 cell cycle arrest or S-phase block after IR or cisplatin, respectively.
- TICs exhibited increased γH2AX at baseline, and diminished DNA damage-induced phosphorylation of DNA-PK, ATM, KAP-1 and H2AX.
- Analysis of phosphorylated receptor tyrosine kinases displayed lower IGF1R phosphorylation and expression and a higher degree of ERK phosphorylation in TICs as compared to bulk cells.
- MEK inhibition reduced TIC viability alone and decreased clonogenicity upon IR suggesting that MEK and downstream signaling impart on TIC radiation response.
- We demonstrate that reduced apoptotic response, less pronounced cell cycle arrest, altered DNA repair and receptor tyrosine kinase signaling in NSCLC TICs are possible factors contributing to their therapy resistance.

References