to identify the potassium channels that could be implicated in the response to TNF.

**Material and methods** We analysed the effects of TNF on two CRC cell lines, HCT116 that is KRAS mutated and HT29 that is KRAS wildtype. Cell lines viability and migration were determined by MTT assay and scratch assay, respectively. Cell cycle was examined by propidium iodide DNA staining. Gene expression of TNF pathway and potassium channels was measured by RTqPCR and Western blot.

**Results and discussions** Our work shows that TNF increased the migration of HT29 cells while reducing that of HCT116. In addition, TNF reduced the viability of HCT116 cells and their colony formation capacity. Moreover, cell cycle analyses showed an increase in the proportion of sub-G1 phase in HCT116 cells after TNF treatment, with no effect on HT29 cells. We also demonstrated an increased expression and phosphorylation of STAT3 protein in HT29 cells, contrary to HCT116 cells that showed reduced phosphorylation following TNF treatment. Interestingly, exogenous TNF increased the transcriptional expression of TNF in both cell lines and this result was associated with an increased expression of its receptor, TNFR2, only in HT29 whereas it was abrogated in HCT116 cells. Furthermore, TNF caused a global decrease in the expression of potassium channels coding genes in HCT116 cells, while this effect was less pronounced in HT29 cells.

**Conclusion** Taken together, our results suggest that the modulation of TNF pathway could be associated to KRAS status. Furthermore, potassium channels could be implicated in CRC cells response to TNF.

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**PO-043**

**TARGETING THE THIOL OXIDOREDUCTASES ERP57 AND PDI HITS CANCER CELLS ON MULTIPLE FRONTS: PROLIFERATION, RADIORESISTANCE AND ER STRESS RESPONSE (UPR)**

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**Introduction** Fast-growing tumour cells show enhanced protein synthesis and therefore depend on efficient folding for nascent export proteins in the endoplasmic reticulum (ER). Herein, the two most prominent ER resident thiol oxidoreductases ERP57 and PDI play important parts in formation of disulfide bonds in client proteins. This and the finding that both proteins fulfil various roles also in other compartments (i.e. cytoplasm, nucleus, cell membrane) encouraged us to investigate the impact of their depletion on colorectal cancer cells.

**Material and methods** Using an inducible knockdown (KD) system we tested ERP57 and PDI deficiency in long term survival assays in normoxia and hypoxia combined with irradiation.

**Results and discussions** KD of ERP57 or PDI triggered a severe attenuation of proliferation, but only ERP57 deficiency led to activation of the PERK-dependent UPR and apoptosis. When combined with an ERP57 KD, irradiation displayed the most dramatic growth reduction even under 1% oxygen. The absence of ERP57 reduced expression of cellular proliferation factors like c-Myc, PLK-1, AKT, PDK1, ERK1,2 and others.

Further, we demonstrated for the first time that PDI is an essential activator of the ER stress sensor PERK that enforces cancer cell survival under global ER stress in hypoxia. In the absence of ER stress, ERP57 functions as a reductase for PDI that keeps PERK in an inactive state.

**Conclusion** Our data identified ERP57 and PDI as promising new targets for a mono- and combination anti-cancer therapy due to multiple cellular points of attack.