

AG Tumorbiochemie

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Stress defence and phenotypic reprogramming in melanoma

Our group investigates the tumor adaptation processes in defence to stress, which melanoma cells encounter e.g. in the tumor niche or after exposure to therapeutics.

One focus is the oxidative stress defence, which is maintained in melanoma by a pronounced utilization of enzymes involved in cysteine supply - an important prerequisite for glutathione - and by the upregulation of enzymes involved in the detoxification of peroxides (Schmitt et al., 2015; Meierjohann et al., 2014; Leikam et al., 2014; Lokaj et al., 2009).

Oxidative stress leads to an upregulation of the master regulator of the oxidative stress response, NRF2. We recently described that NRF2 plays a dual role in melanoma: on the one hand, it expectedly protects the cells from oxidative damage by upregulating genes involved in glutathione and thioredoxin synthesis and regeneration. On the other hand, NRF2 enables a transcriptional switch by blocking the melanocytic lineage factor MITF and therefore the expression of differentiation antigens and by elevating the MITF counterplayer FRA1, which has a tumor-promoting function in melanoma (Jessen et al., 2020; Maurus et al., 2017). Furthermore, we identified NRF2 as potent trigger for the expression of cyclooxygenase 2 (COX2) and the consequential secretion of prostaglandin E2, thereby limiting the type I interferon response and promoting an immune-tolerant tumor microenvironment. Thus, NRF2 serves as emergency transcription factor in melanoma, which combines oxidative stress defence with the protection from the immune system (Figure 1).

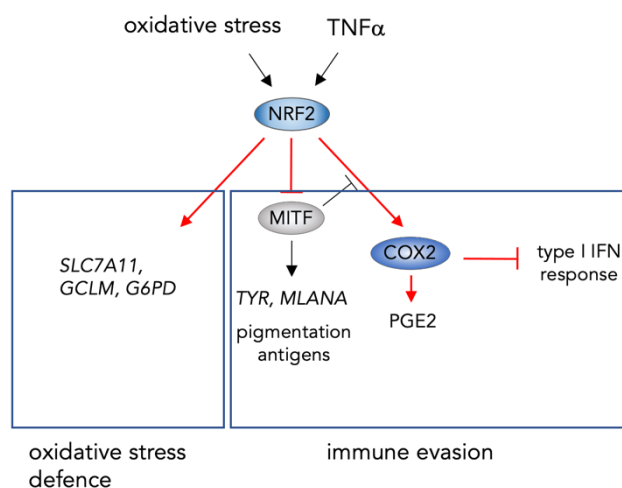


Figure: Overview of triggers and effectors of NRF2 in melanoma.

NRF2 can be induced by oxidative stress or the cytokine TNF α in melanoma. This leads to the induction of classical NRF2 target genes such as SLC7A11 (cystine/glutamate antiporter), GCLM (glutathione synthesis), and G6PD (NADPH regeneration). Furthermore, NRF2 blocks the activity of MITF, leading to a reduced expression of pigmentation antigens. Also, the reduction of MITF activity contributes to enhanced COX2 expression, thus triggering immune-evasive properties.

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