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The zebrafish: a new model to understand the crosstalk between inflammation and cancer

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Inflammation is well known to play an essential role in cancer development. The zebrafish is a unique model to study in vivo the interplays between inflammation and tumor development, since the interactions between immune, tumor and endothelial cells can be visualized at real-time in a whole vertebrate organism. Using this model, we evaluated the impact of BCL-xL/CXCL8 axis in promoting human melanoma angiogenesis and aggressiveness *in vivo* by using xenotransplantation assay in *tg(fli1a:EGFP)* embryos, which have green fluorescent blood vessels. We found that BCL-xL enhanced melanoma cells dissemination and angiogenesis through the release of CXCL8. Interestingly, BCL-xL-enhanced dissemination was mediated by an autocrine signaling via CXCR2 rather than by CXCL8 receptor-mediated paracrine signaling. Furthermore, we have also developed a model to study the role of oxidative stress in melanoma progresssion by crossing the line *tg(kita:HRASV12)*, which develops spontaneous melanomas, with a line *tg(kita:DN-Duox1)*, which express a dominant negative form of the H_2O_2-producing enzyme Dual oxidase 1 (Duox1). We found that Duox1 was necessary to inhibit the progression from benign nevus to malignant melanoma as well as melanoma progression in allotransplantation assays. Notably, clinical data showed that DUOX1 was strongly silenced when progressing from normal skin and benign nevi to malignant melanoma and its promoter was heavily methylated in tumour samples, suggesting that its downregulation might be necessary for melanoma establishment. Paradoxically, in melanoma patients both low and high expression was correlated with bad prognosis. In addition, DUOX1 expression was associated to the immune response and increased oxidative stress, cell proliferation and angiogenesis; these signaling pathways being all relevant for melanoma aggressiveness. Collectively, our results highlight the usefulness of the zebrafish to study the crosstalk between inflammation and cancer, and reveal new prognosis markers and therapeutic targets for melanoma.