The role of BRAFE600-induced senescence in tumour suppression

Michaloglou, C.

2010

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Summaries

Summary

The role of $BRAF^{E600}$-induced senescence in tumour suppression

At the cellular level, cancer is the result of uncontrolled cell division, which is most commonly achieved by the activation of oncogenes and the loss of tumour suppressor genes. However, the cellular stress caused by oncogenic transformation can, in particular in early tumour cells, induce apoptosis, thereby eliminating cells at risk of transformation. As such, apoptosis is considered to be a critical cell-intrinsic tumour suppressive mechanism limiting tumourigenic expansion. Besides the induction of apoptosis, oncogenic activation in mammalian cells *in vitro* can also induce a permanent cell cycle arrest, termed oncogene-induced senescence. Originally identified as a result of the ectopic expression of oncogenic HRAS (RasV12), oncogene-induced senescence has now been demonstrated to occur for a variety of oncogenes and inactivated tumour suppressor genes. In many cases, its induction *in vitro* depends on the presence of intact tumour suppressor pathways such as the p53 and RB pathways. More recently, oncogene-induced senescence has been recognized also as a cancer-preventing mechanism *in vivo*. As many important questions have as yet remained unanswered, oncogene-induced senescence and its relevance for tumour suppression have been the subject of much research and debate.

The BRAF protein kinase is a RAS effector and is frequently mutated in a variety of human cancers, including melanoma. Strikingly, it is also commonly found mutated in human naevi, benign tumours of melanocytic origin. The first chapter describes the role of BRAF in oncogenic transformation and senescence in humans. It provides an overview of the prevalence of BRAF mutations in human tumours and an introduction to oncogene-induced senescence, as well as a description of the characteristics of benign human lesions, and in particular naevi.

The presence of an oncogene in benign human tumours containing non-proliferating cells, that show induced expression of the tumour suppressor $p16^{INK4A}$, led us to hypothesise that human naevi undergo oncogene-induced senescence. Thus, we postulated that oncogenic BRAF is capable of inducing a senescence-like phenotype both *in vivo* and *in vitro*. In the second chapter, we provide evidence supporting this idea that oncogenic BRAF induces senescence in primary human melanocytes and fibroblasts, and show that this is accompanied by the induction of the melanoma-associated tumour suppressor $p16^{INK4A}$. Furthermore, by showing the accumulation of senescence markers in human naevi, we provide the first evidence for the presence of

senescence *in vivo*, in a benign human lesion.

In an attempt to dissect the underlying mechanism, we set out to identify the mediators of BRAF-induced senescence. We studied the role of the melanoma-related tumour suppressors $p16^{INK4A}$ and $p15^{INK4B}$ in the onset of senescence (chapters 2 and 3). We find that although both proteins are induced by oncogenic BRAF, they are dispensable for the concomitant induction of cell cycle arrest. In chapter 4, we identify a link between the induction of $p16^{INK4A}$ and $p15^{INK4B}$. We find that $p16^{INK4A}$ can regulate $p15^{INK4B}$ levels post-transcriptionally, indicating a compensatory mechanism between $p16^{INK4A}$ and $p15^{INK4B}$ in human cells. Finally, in chapter 5 we provide an overview of our current knowledge on cellular senescence and give a detailed description of replicative and premature senescence. Moreover, we discuss the signals leading to cellular senescence as well as give a critical overview of the currently available biomarkers for the detection of senescence *in vitro* and *in vivo,* in mammalian cells.

The research described in this thesis provides one of the first pieces of evidence supporting the existence of oncogene-induced senescence *in vivo* and its role as an intrinsic tumour-suppressing mechanism in humans. Although the findings in this thesis have no immediate therapeutic application, they contribute to our understanding of a process that may be exploited for the treatment of cancer in the future

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