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IKKβ overexpression together with a lack of tumour suppressor genes causes ameloblastic odontomas in mice

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Odontogenic tumours are a heterogeneous group of lesions that develop in the oral cavity region and are characterized by the formation of tumoural structures that differentiate as teeth. Due to the diversity of their histopathological characteristics and clinical behaviour, the classification of these tumours is still under debate. Alterations in morphogenesis pathways such as the Hedgehog, MAPK and WNT/β-catenin pathways are implicated in the formation of odontogenic lesions, but the molecular bases of many of these lesions are still unknown. In this study, we used genetically modified mice to study the role of IKKβ (a fundamental regulator of NF-κB activity and many other proteins) in oral epithelial cells and odontogenic tissues. Transgenic mice overexpressing IKKβ in oral epithelial cells show a significant increase in immune cells in both the oral epithelia and oral submucosa. They also show changes in the expression of several proteins and miRNAs that are important for cancer development. Interestingly, we found that overactivity of IKKβ in oral epithelia and odontogenic tissues, in conjunction with the loss of tumour suppressor proteins (p53, or p16 and p19), leads to the appearance of odontogenic tumours that can be classified as ameloblastic odontomas, sometimes accompanied by foci of secondary ameloblastic carcinomas. These tumours show NF-κB activation and increased β-catenin activity. These findings may help to elucidate the molecular determinants of odontogenic tumourigenesis and the role of IKKβ in the homoeostasis and tumoural transformation of oral and odontogenic epithelia.

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INTRODUCTION

The IKK complex is responsible for the regulation of the NF-κB family of transcription factors, which regulates genes associated with cell survival and increased proliferation. Deregulated NF-κB activation underlies disease states in many organs, including chronic inflammation and cancer. The IKK complex is formed by two catalytic subunits with kinase activity (IKKα and IKKβ) and one regulatory subunit (IKKγ or NEMO).[1] In addition to the role of IKKβ as a positive regulator of NF-κB activity, it interacts with, phosphorylates, and thereby modifies the activity of a plethora of proteins implicated in a number of functions.[1,2] Furthermore, it has recently been reported that the IKK complex acts as a general regulator of gene expression by modifying mRNA stability.[3] Thus, IKKβ is able to regulate cellular physiology in different ways and, not surprisingly, changes in the activity of IKKβ are associated with cancer in several cell types. Interestingly, IKKβ can either promote or prevent tumour development, depending on the cell type and other circumstances that are not yet well understood, probably due to the large number of proteins regulated by this kinase.[4]

Previously, we generated transgenic mice overexpressing IKKβ in basal cells of the stratified epithelia and in exocrine glands. In addition to other phenotypes, IKKβ overexpression in these mice led to greater numbers of $CD45^+$ haematopoietic cells as well as granulocytes ($Gr\text{-}1^+$), macrophages ($F4/80^+$) and B cells ($B220^+$) in the forestomach epithelium[5] and to the development of supernumerary teeth due to reduced apoptosis and upregulation of the WNT signalling pathway in the embryonic incisor bud epithelium of K5-IKKβ mice.[6] Carcinogenesis experiments performed in a genetic background prone to tumour development through the expression of an active form of RAS revealed that K5-IKKβ mice are resistant to skin cancer,[7] but they develop more malignant tumours than control littermates in the forestomach and the palate.[5] In the course of these experiments, we crossed the K5-IKKβ transgene into backgrounds lacking p53 in epithelial cells ($p53^{EKO}$/K5-IKKβ mice) or lacking p16 and p19 in every cell (*Ink4a/Arf* ^{KO}/K5-IKKβ). Surprisingly, a high percentage of these mice developed spontaneous odontogenic tumours.

Odontogenic tumours are a heterogeneous group of lesions of the oral cavity that result in the formation of tumoural structures that differentiate as teeth. Their classification is still under debate and has been recently modified by the World Health Organization.[8] These lesions are currently classified as odontogenic cysts and odontogenic tumours (benign or malignant), and each of these categories is in turn classified into a number of

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