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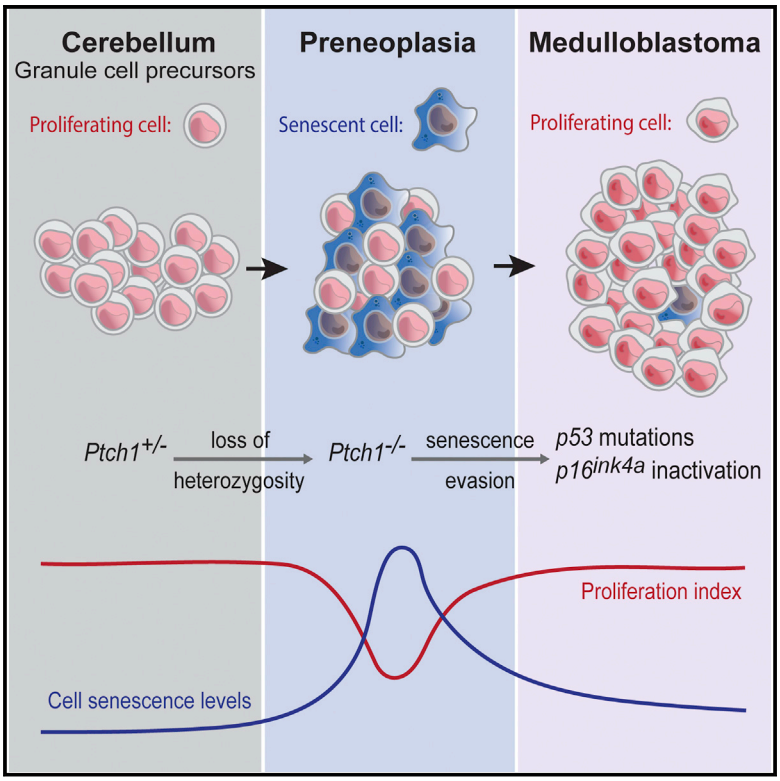
Cell Reports

Evasion of Cell Senescence Leads to Medulloblastoma Progression

Graphical Abstract



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In Brief

How brain tumors develop from precancerous lesions is not well understood. Using *Ptch1* heterozygous mice, Tamayo-Orrego et al. show that medulloblastoma preneoplastic lesions display *Ptch1* loss of heterozygosity and cell senescence, a tumor-suppressive mechanism. Subsequently, spontaneous *p53* mutations or *p16ink4a* inactivation leads to senescence evasion and medulloblastoma progression.

Highlights

- Medulloblastoma preneoplastic lesions exhibit *Ptch1* loss of heterozygosity
- Medulloblastoma preneoplasia display high levels of cell senescence
- Spontaneous *p53* mutations or *p16ink4a* inactivation leads to senescence evasion
- Cell senescence is a tumor-suppressive mechanism for medulloblastoma

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Evasion of Cell Senescence Leads to Medulloblastoma Progression

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SUMMARY

How brain tumors progress from precancerous lesions to advanced cancers is not well understood. Using *Ptch1*$^{+/-}$ mice to study medulloblastoma progression, we found that *Ptch1* loss of heterozygosity (LOH) is an early event that is associated with high levels of cell senescence in preneoplasia. In contrast, advanced tumors have evaded senescence. Remarkably, we discovered that the majority of advanced medulloblastomas display either spontaneous, somatic *p53* mutations or *Cdkn2a* locus inactivation. Consistent with senescence evasion, these *p53* mutations are always subsequent to *Ptch1* LOH. Introduction of a *p53* mutation prevents senescence, accelerates tumor formation, and increases medulloblastoma incidence. Altogether, our results show that evasion of senescence associated with *Ptch1* LOH allows progression to advanced tumors.

INTRODUCTION

For a certain number of human malignancies, it has been possible to examine different stages of tumor progression and correlate different histopathological stages with specific genetic events (Fearon and Vogelstein, 1990). More recently, an emerging paradigm proposes that oncogenic changes associated with the formation of precancerous lesions lead to cell senescence, a mechanism that restrains tumor progression in vivo (Braig et al., 2005; Chen et al., 2005; Michaloglou et al., 2005). Brain tumors constitute a challenge for investigating tumor progression because precancerous lesions are rarely detected. Medulloblastoma is the most common brain tumor in children, and deregulation of hedgehog signaling characterizes 25% of human medulloblastomas (Taylor et al., 2012). Although genomic studies have revealed recurrent genetic and epigenetic alterations in human sonic hedgehog (SHH) medulloblastoma (Hovestadt et al., 2014; Kool et al., 2014; Pugh et al., 2012; Robinson et al., 2012), these studies can only be done on advanced tumors and thus they do not illuminate the process of medulloblastoma progression.

Ptch1 heterozygous mice (*Ptch1*$^{+/LacZ}$, designated here as *Ptch1*$^{+/-}$ for simplicity) constitute one of the best-studied models of medulloblastoma (Goodrich et al., 1997). It is currently accepted that medulloblastoma development in *Ptch1*$^{+/-}$ mice is a two-step process in which the *Ptch1*$^{+/-}$ germline mutation leads to preneoplasia formation and the subsequent *Ptch1* loss of heterozygosity (LOH) is sufficient to promote medulloblastoma progression (Ayrault et al., 2009; Pazzaglia et al., 2006). Consistent with this, human genomic studies indicate that medulloblastoma, similar to other pediatric cancers, displays few molecular changes compared to other types of tumors (Pugh et al., 2012). Nevertheless, one study reported that preneoplastic cells with *Ptch1* LOH can differentiate into granule neurons (Kessler et al., 2009), raising the possibility that *Ptch1* LOH is not sufficient to promote medulloblastoma progression and that there may be additional genetic or epigenetic events governing the transition from preneoplasia to medulloblastoma.

Using the *Ptch1* model of medulloblastoma, we discovered that *Ptch1* LOH is a very early event during medulloblastoma development and is associated with high levels of cell senescence in preneoplastic lesions. Additionally, we found that advanced tumors have evaded cell senescence as a result of *p53* mutations or *Cdkn2a* locus inactivation, which occurs via methylation of p16^{Ink4a}/*Cdkn2a* regulatory sequences. Using orthotopic transplantation and genetic experiments, we show that *p53* point mutations prevent cell senescence, accelerate tumor formation, and increase medulloblastoma incidence. Altogether, we propose that medulloblastoma formation requires at least three genetic events, where *p53* or *Cdkn2a* inactivation disables