Unifying the p73 knockout phenotypes: TAp73 orchestrates multiciliogenesis

Marco Napoli[1,2] and Elsa R. Flores[1,2,3]

[1]Department of Molecular and Cellular Oncology, [2]Department of Translational Molecular Pathology, [3]Graduate School of Biomedical Sciences, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA

Multiciliogenesis is essential for the function of different epithelia, and its failure results in brain defects, respiratory diseases, and infertility. In this issue of *Genes & Development*, Nemajerova and colleagues (pp. 1300–1312) reveal the *p53* family member and *p73* isoform TAp73 as a transcription factor dictating the differentiation of multiciliated cells. Their findings provide the long-awaited unifying explanation for the diverse phenotypes of the *p73* knockout mice.

Motile cilia are specialized organelles present on many epithelia, and defects in these structures cause respiratory diseases, otitis, infertility, and hydrocephalus (Fliegauf et al. 2007). These disorders are reminiscent of the phenotypes of $p73^{-/-}$ mice, which include hippocampal dysgenesis, severe hydrocephalus, sterility, and chronic infections in the airways (Yang et al. 2002). *p73* belongs to the p53 family of transcription factors, which also includes *p63*. Compared with the spontaneous tumor development in the $p53^{-/-}$ mice and the epidermal defects in the $p63^{-/-}$ mice (Yang et al. 2002), the effects of *p73* loss are more diverse, and a unifying mechanism has long been sought. Now, based on the striking similarities in the phenotypes of $p73^{-/-}$ mice to mice devoid of the master regulator of the motile cilia *Foxj1* (Brody et al. 2000), Nemajerova et al. (2016) investigated the possible involvement of p73 in multiciliogenesis. Through a thorough analysis of the airways, they found fewer and shorter motile cilia in $p73^{-/-}$ mice compared with their wild-type counterparts. The subsequent accumulation of exogenous factors in the lungs of $p73^{-/-}$ mice led to macrophage recruitment, chronic bronchitis, and secondary emphysema. Since *p73* encodes two sets of isoforms, TAp73 isoforms with an N-terminal transactivation domain and ΔNp73 isoforms lacking this domain, the investigators inspected tracheas and bronchi of *TAp73* isoform-specific knockout mice and found that they phenocopied the $p73^{-/-}$ mice, thus implicating *TAp73* in multiciliogenesis. These alterations are in line with the spontaneous lung adenocarcinoma predisposition in $p73^{+/-}$ and $p73^{-/-}$ mice (Flores et al. 2005) and $TAp73^{-/-}$ mice (Tomasini et al. 2008). To ascertain the underlying molecular mechanism, Nemajerova et al. (2016) performed RNA sequencing analysis of wild-type and $p73^{-/-}$ tracheal epithelial cells. These genome-wide data showed that p73 affected the expression of 50 genes required for ciliary formation and motility, eight of which are found mutated in human ciliopathies (Fliegauf et al. 2007). Importantly, this set of genes included key ciliogenic transcription factors whose control by TAp73 was also confirmed in human cells, therefore establishing the evolutionary conservation of this regulation. One of these TAp73 direct target genes, *Foxj1*, was able to rescue the ciliary defects when overexpressed in $p73^{-/-}$ tracheal epithelial cells, thus indicating that TAp73 is a central regulator of multiciliogenesis acting upstream of *Foxj1*.

A direct link between p73 and Foxj1 was also recently published by the Pietenpol laboratory (Marshall et al. 2016). They found defects in *p73*-deficient multiciliated cells in several organs and that p73 could only be detected in 50% of basal cells of the trachea, where it colocalized with its family member and basal cell marker p63. Interestingly, in $p73^{-/-}$ tracheas, the percentage of basal cells was lower than in wild-type mice, and the ratio among the differentiated cell types was altered, thus implying that loss of *p73* profoundly affected basal cell maintenance and differentiation.

Both of these studies greatly advance our comprehension of multiciliogenesis regulated by p73 and provide a unifying explanation for the variegate phenotypes of the $p73^{-/-}$ mice (Fig. 1). At the same time, these studies raise several questions regarding the interactions of the p53 family members in lung biology. In particular, what are the different biological functions of the $p63^{+}/p73^{+}$ basal cells compared with the $p63^{+}$ ones? Furthermore, even though the Moll group (Nemajerova et al. 2016) demonstrated TAp73 requirement in multiciliogenesis, does

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Corresponding author: elsaflores@mdanderson.org
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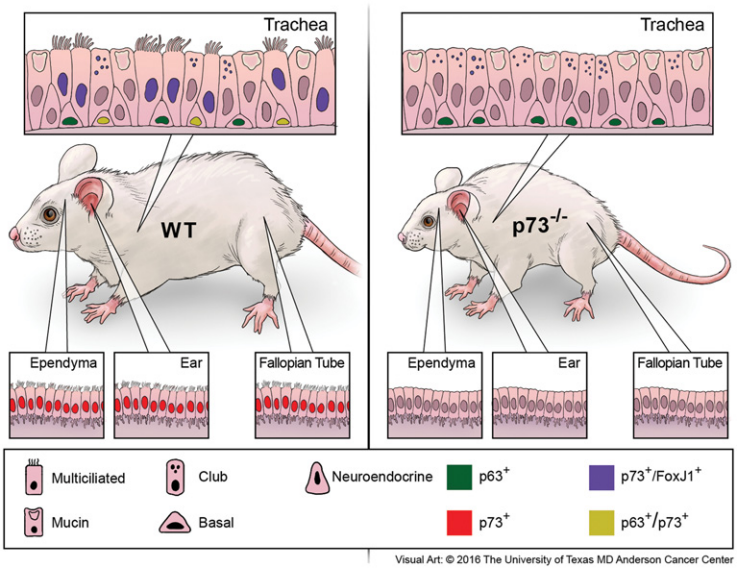

Figure 1. The phenotypes of the $p73^{-/-}$ mice reveal p73 as a master regulator of multiciliogenesis. Wild-type mice express p73 (red) in multiciliated cells of different organs. In the trachea, p73 is expressed in 50% of basal cells with p63 (yellow) and in all of the multiciliated cells with Foxj1 (purple). All of the remaining cells are *p73*-negative (gray nuclei).

ΔNp73 have a role too? Finally, given that TAp63 and TAp73 can also have overlapping functions (Napoli and Flores 2013) and that both p63 and p73 regulate cilia-associated genes (Marshall et al. 2016), is TAp63 involved in multiciliogenesis? Addressing these questions will be essential to elucidate the isoform-specific roles and the interplay of the p53 family members in lung physiology and diseases.

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