

P63, A Master Regulator of Epithelial Cancer and a Squamous Cell Carcinoma Driver

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Commentary

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all cases of lung cancer, and is sub-classified mainly into adenocarcinoma (AC) and squamous cell carcinoma (SCC) [1]. Current treatment strategies for NSCLC depend on the histological tumor subtypes and molecular targeted agents for targetable genome alterations. Although there have been significant advances in the treatment of NSCLC, therapeutic improvements in the treatment of lung SCC have lagged behind for AC, and further prognostic progresses are needed to enable identification of SCC specific molecules or genomic alterations that could be beneficial for biomarkers and therapeutic targets [2]. While several immunohistochemical markers have been improved for their utility in distinguishing lung SCC from lung AC, the Δ Np63 (p40) is a highly specific marker for lung SCC [3-5].

p63, a member of the p53 family, has significant homology with p53 and regulates crucial events in the proliferative potential of epithelial stem cells and the normal epidermal stratification development [6]. Alternative splicing of the TP63 gene generates transcripts encoding two opposing functions of isoforms with the transactivation domain (TAp63) and without the domain (Δ Np63) [7-9]. The splicing at the 3' end of p63, resulting in the isoforms α , β and γ [7,9,10]. Early studies showed that Δ Np63 acts as a dominant-negative transcriptional repressor to inhibit p53- or p63-mediated transcription in vitro and in vivo, consistent with a potential oncogenic role for the Δ Np63 isoform [8,11]. However, the Δ Np63 isoform also has transcriptional activity that is independent of the second transactivation domain [12]. Although TAp63 and Δ Np63 shows overlapping distributions in some epithelial tissues, Δ Np63 is more expressed in basal cells, suggesting that single expression of Δ Np63 is correlated with the cancer stem-like cell populations and that the distinct patterns of p63 isoforms may contribute to epithelial proliferation and differentiation [13,14].

The genomic regions of the p63 gene are frequently amplified and the levels of p63 are sometimes altered in a variety of epithelial cancers, including lung SCC, head and neck SCC, bladder cancer, breast cancer and cervical cancer [4,13,15,16]. Although the genomic region containing the TP63 gene is frequently amplified in SCCs, the expression levels of p63 are also regulated by ubiquitin-mediated proteolysis by E3 ubiquitin ligases, such as Nedd4 [17], Itch [18], FBW7 [19] and Pirh2 [20]. The levels of Δ Np63 proteins are also regulated in a coordinated manner by two scaffold proteins, Syntaxin Binding Protein 4 (STXBP4) and Receptor of activated kinase C1 (RACK1), which directly interact with Δ Np63 [21,22].

Newly reported that STXBP4 plays a positive regulator of Δ Np63 stability for enhanced oncogenic potential through Platelet-Derived Growth Factor Receptor α (PDGFR α) signaling in a Δ Np63-dependent manner in lung SCC [21,23], although STXBP4 is originally identified as a glucose transporter [24,25]. In line with this result, the inhibition of the complex formation between p53 and NF-Y by gain-of-function (GOF) of mutant p53 enhances PDGFR β expression and promotes metastasis in a subset of pancreatic cancers [26]. In addition, an interaction of p63 with mutant p53 regulates the expression of p63 target genes to enhance invasion and metastasis [27]. Hence, the oncogenic activity of mutant p53 may be dependent on the physical association between p63 and mutant p53.

Despite p63, a master regulator of epithelial cells, is regulated by the multiple signaling pathways that could contribute to several epithelial cancers, such as the Wnt, FGFR and EGFR pathways [15,28,29], p63 expression is also reported to be decreased during progression to invasion and metastasis, and the loss of p63 expression is associated with poor prognosis in some cases [29-31]. It could be the balance between the TA isotype as a tumor suppressor and Δ N isotype as an oncogene, as well as the tissue context, which is critical for proliferation and differentiation in both epithelial stem cells and cancer stem cells. These issues highlight the growing importance of accurate identification of SCC treatment for assigning patients to appropriate histology-based therapies and the triage of tissue for appropriate molecular studies.

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