Molecules and Cells

Minireview

Oncogenic RUNX3: A Link between p53 Deficiency and MYC Dysregulation

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The RUNX transcription factors serve as master regulators of development and are frequently dysregulated in human cancers. Among the three family members, RUNX3 is the least studied, and has long been considered to be a tumor-suppressor gene in human cancers. This idea is mainly based on the observation that RUNX3 is inactivated by genetic/epigenetic alterations or protein mislocalization during the initiation of tumorigenesis. Recently, this paradigm has been challenged, as several lines of evidence have shown that RUNX3 is upregulated over the course of tumor development. Resolving this paradox and understanding how a single gene can exhibit both oncogenic and tumor-suppressive properties is essential for successful drug targeting of RUNX. We propose a simple explanation for the duality of RUNX3: p53 status. In this model, p53 deficiency causes RUNX3 to become an oncogene, resulting in aberrant upregulation of MYC.

Keywords: c-Myc, p53, RUNX3

INTRODUCTION

The Runt-related transcription factor (RUNX) family consists of three members, which share the highly conserved 'Runt' DNA-binding domain that associates with their co-factor, core binding factor β (CBFβ). All three RUNX proteins and CBFβ exert tumor-related functions in context-dependent manners. RUNX3 is the least studied member of the family, as it has been reported to act as both a tumor-suppressor and oncogene in human cancers. Initially, its broad tumor-suppressive function attracted attention, originating from observations of gastric phenotypes in *Runx3*-knockout mice and the causal relationship between *RUNX3*-silencing and human gastric cancer (Li et al., 2002). RUNX3 inactivation occurs due to genetic/epigenetic alteration or protein mislocalization in a diverse range of human cancers, including gastric, colorectal, lung, pancreas, breast, liver, and prostate cancers as well as leukemia and neuroblastoma. On the other hand, RUNX3 upregulation has been observed in various cases of human malignant tumors, suggesting that it plays oncogenic roles (Chuang et al., 2017; Ito et al., 2015). In these cases, RUNX3 stimulates cell proliferation, inhibits apoptosis, confers drug resistance, and promotes tumorigenicity in human cancers (Table 1), implying that oncogenic RUNX3 is related to tumor malignancy, invasiveness and metastasis.

The past two decades of RUNX3 research have further clarified its original tumor-suppressive functions, but have also elaborated its opposing roles as an oncogene, provoking an essential question: how is the dual nature of RUNX3 determined by cellular context? Given the potential medical value of targeting the RUNX transcription factors, the demand for an answer to this question continues to grow (Bushweller, 2019; Cunningham et al., 2012; Morita et al., 2017). As we will show below, RUNX3 acts as a tumor-suppressor when interacting with p53, but as a tumor promoter when associ-

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Table 1. Oncogenic functions of RUNX3 reported so far

Cancer type	Oncogenic RUNX3 functions	References
AML	Drug resistance acquisition	(Damdinsuren et al., 2015)
T-ALL	Apoptosis inhibition	(Choi et al., 2017)
Basal cell carcinoma	Cell growth stimulation	(Lee et al., 2011a)
Head and neck cancer	Cell growth stimulation	(Tsunematsu et al., 2009)
Ovarian cancer	Tumorigenicity enhancement Drug resistance acquisition Cell growth stimulation	(Barghout et al., 2015; Chen et al., 2019; Lee et al., 2011b; Nevadunsky et al., 2009)
Pancreatic cancer	Metastasis promotion *in vivo*	(Whittle et al., 2015)
Ewing's sarcoma	Tumorigenicity enhancement	(Bledsoe et al., 2014)

ating with MYC. These observations led us to focus on p53 and MYC, two central figures in tumor development, as contextual determinants of the duality of RUNX3.

RUNX3 AND p53

RUNX3 acts as a positive regulator for p53, the quintessential gatekeeper and guardian of the genome, under two circumstances: upon DNA damage or upon oncogene activation (Bae et al., 2019; Lee et al., 2017). In the former case, RUNX3 is induced by DNA damage, forms a complex with p53, and facilitates its modifications (i.e., phosphorylation at Ser-15), thereby stabilizing p53 activity and promoting apoptosis (Ozaki et al., 2013; Yamada et al., 2010). On the other hand, RUNX3 is also activated by oncogenic KRAS and indirectly stabilizes p53 by transcriptionally upregulating *p14ARF* (*p19Arf* in mice; hereafter *ARF*) in collaboration with pRB and BRD2, serving as a counterbalance to MDM2-mediated p53 degradation (Lee et al., 2013; 2019). Importantly, whether it is invoked by DNA damage or oncogenic stress, the tumor-suppressive functions of RUNX3 seem to be largely dependent on an intact p53 pathway.

Another oncogenic stress that invokes the ARF–p53 pathway is MYC (Eischen et al., 1999; Murphy et al., 2008; Phesse et al., 2014; Schmitt et al., 1999; Zindy et al., 1998), a master regulator of cell proliferation broadly involved in the pathogenesis of human cancer. Indeed, MYC transcriptionally activates RUNX3 in NKTL (natural killer/T-cell lymphoma) cells (Selvarajan et al., 2017), suggesting that MYC, as well as KRAS, is one of the oncogenes that trigger the RUNX3–ARF–p53 pathway. p53 protects against MYC either directly, by transcriptional repression (Ho et al., 2005; Porter et al., 2017), or indirectly, via miR-145 induction (Sachdeva et al., 2009). Moreover, *MYC*-driven lymphomagenesis *in vivo* is dramatically increased by *p53* disruption (Blyth et al., 1995; Eischen et al., 1999; Schmitt et al., 1999) and inhibited by *p53* restoration (Martins et al., 2006).

Once activated by RUNX3, p53 seems to repress RUNX3 function. Aberrant upregulation of Runx3 coincides with the apparent loss of heterozygosity (LOH) of *p53* in a pancreatic cancer model, the *Kras*$^{LSL\text{-}G12D/+}$;*p53*$^{LSL\text{-}R172H/+}$;*p48Cre* (*KPC*) mice (Whittle et al., 2015). *Runx3* and *Runx1* mRNA levels are upregulated upon *p53*-knockout in some primary mesenchymal cells (Shimizu et al., 2013). Also, Runx2 expression increases upon inactivation of p53 in both primary osteoblasts and bone marrow mesenchymal stromal cells (He et al., 2015; Lengner et al., 2006; Shin et al., 2016). In terms of mechanism, miR-34, one of the best studied miRNAs induced by p53 (He et al., 2007; Okada et al., 2014), downregulates expression of *Runx3* (Rodriguez-Ubreva et al., 2014) and *Runx2* (He et al., 2015; van der Deen et al., 2013). RUNX3 contributes to the functional activity of p53 either directly, by binding it, or indirectly, via *ARF* induction, but excessive p53 activity would doubtless lead to undesired side effects.

If the tumor-suppressive functions of RUNX3 are governed by p53 in this manner, p53 inactivation might be the very event that triggers Runx3 dysregulation and its conversion to an oncogene. In fact, upregulation of Runx3 in *KPC* mice in which *p53* has undergone LOH facilitates pancreatic cancer metastasis (Whittle et al., 2015). Also, upon p53 loss, Runx1 accelerates tumorigenicity in mouse embryonic fibroblast cells (Wotton et al., 2004), and heterozygous deletion of *Runx1* in *p53*-null mice decreases the incidence of thymic lymphoma, thus lengthening their lifespans (Shimizu et al., 2013). In addition, *Runx2*-induced lymphomagenesis shortens the lifespans of *p53*-null mice, but no such effect is observed in *p53*-heterozygous mice (Blyth et al., 2001).

p53 hotspot mutations might also contribute to the oncogenic conversion of Runx3. p53 hotspot mutants, exemplified by p53^{R175H} (p53^{R172H} in mice), possess oncogenic (gain-of-function) properties in addition to defects in tumor suppression (Donehower and Lozano, 2009). As mentioned above, wild-type p53 promotes its own tumor-suppressive activities by directly interacting with RUNX3, whereas p53 hotspot mutants do not follow suit. On the contrary, it is suggested that p53^{R175H} is also capable of directly interacting with RUNX3, and that the p53^{R175H}–RUNX3 complex is aberrantly stable and exerts its oncogenic activities by altering the transcriptional targets of each of its components (Whittle and Hingorani, 2017; Whittle et al., 2015). In fact, p53^{R175H} is involved in the switching of transforming growth factor β (TGF-β) signaling from a tumor-suppressor to a tumor-promoter (Adorno et al., 2009); TGF-β requires tumor-suppressive RUNX3 to exert some of its anti-tumor effects (Chang et al., 2010; Chi et al., 2005; Ikushima and Miyazono, 2010; Yano et al., 2006). In line with this series of evidence, *p53* deficiency most likely causes oncogenicity of RUNX3 in human carcinogenesis (Fig. 1).

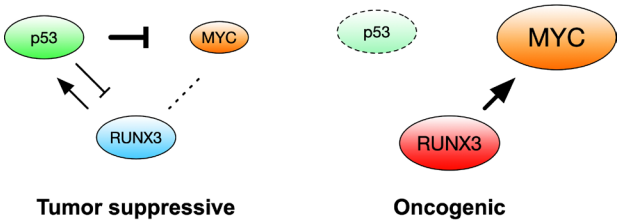

Fig. 1. p53 status as a contextual determinant of the duality of RUNX3. Following DNA damage or oncogenic stress, RUNX3 positively regulates p53 and is in turn suppressed by it; p53 then prevents tumorigenesis by decreasing the activity of crucial oncogenes such as MYC (left). Upon inactivation of p53, dysregulated RUNX3 starts to aberrantly upregulate MYC (right). Thus, p53 status is a contextual determinant for whether RUNX3 behaves as a tumor-suppressor or oncogene.

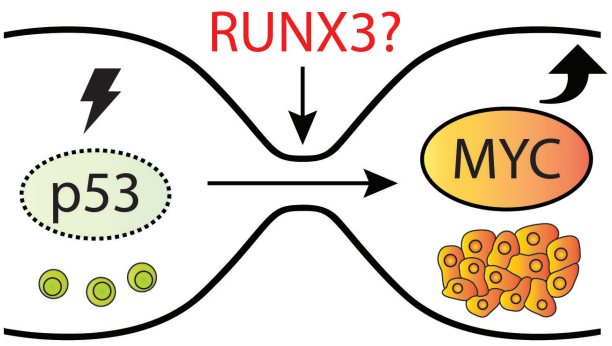

Fig. 2. RUNX3 connects p53 deficiency and MYC dysregulation. Are p53 deficiency and MYC dysregulation, two principal phenomena associated with tumor development, connected by RUNX3?

RUNX3 AND MYC

As listed in Table 1, several lines of evidence have revealed the oncogenic behavior of RUNX3 in multiple types of cancer. Unfortunately, most of these studies have not been able to identify the precise molecular mechanisms underlying the oncogenic phenotypes observed, although these phenotypes can be attributed to aberrant RUNX3 upregulation. We propose that the association of RUNX3 with MYC under p53 deficiency can resolve this enigma.

By retrovirus insertional mutagenesis, all *Runx* family genes have been identified as frequent targets in *MYC*-induced lymphoma (Hay et al., 2019; Neil et al., 2017), and these findings were further corroborated by RUNX proteins' positive correlation with MYC in certain types of leukemia (Choi et al., 2017; Kubota et al., 2019; Selvarajan et al., 2017). In T-cell acute lymphoblastic lymphoma (T-ALL), RUNX3 and RUNX1 bind the +1.43 Mb *MYC* enhancer *N-Me* and upregulate MYC in KOPT-K1 cells (Choi et al., 2017). This long-range distal super enhancer of *MYC*, consisting of multiple RBPJ sites, directly converts aberrant NOTCH1 signaling to MYC dysregulation. *Myc* regulation via *N-Me* is essential for T-cell development and tumorigenesis of *NOTCH1*-induced T-ALL in mice. The relevance of *N-Me* to human T-ALL pathogenesis is supported by the identification of a chromosomal focal amplification at this enhancer in ~5% of human T-ALL cases (Belver and Ferrando, 2016; Herranz et al., 2014). Thus, RUNX3 binding to *N-Me* might at least partly explain its oncogenic contribution to T-ALL development. It should also be noted, however, that in acute myeloid leukemia (AML), RUNX1 and its co-factor CBFβ inhibit MYC expression by binding *BDME*, another *MYC* enhancer 0.4 Mb downstream of *N-Me*, supporting the ideas that RUNX1 plays tumor-suppressive/oncogenic roles on diverse enhancers across leukemia subtypes (Bushweller, 2019; Pulikkan et al., 2018; Shi et al., 2013). Importantly, activation of this RUNX3–MYC axis may depend on p53-deficiency. The major cancer type to which *p53*-deficient mice succumb is thymic lymphoma (Donehower and Lozano, 2009). Moreover, in lymphomas, the most frequently observed somatic alterations are in *CDKN2A* (Ma et al., 2018), which encodes *ARF* and $p16^{INK4A}$, conferring the same benefits as p53 deficiency (Sherr, 2006), and alterations of *TP53* itself is also an independent prognostic indicator (O'Shea et al., 2008; Young et al., 2008).

In bone-related cells, RUNX3 is highly upregulated across several Ewing's sarcoma cell lines and facilitates their cell growth (Bledsoe et al., 2014). Notably in this regard, RUNX2 binds and epigenetically activates the *MYC* regulatory element to induce upregulation of MYC. Indeed, individual knockdown of *RUNX2* or *MYC* abolishes tumorigenicity of SaOS2, a human osteosarcoma cell line (Shin et al., 2016). The same mechanism might be applicable to RUNX3, considering that functions of both Runx2 and Runx3 are required during bone development (Yoshida et al., 2004). Moreover, experiments in osteoblast-specific Runx3-deficient mice clearly showed that Runx3 is non-redundantly required for the proliferation of pre-committed cells to generate adequate numbers of active osteoblasts, whereas Runx2 is mandatory for osteoblastic lineage commitment (Bauer et al., 2015). Importantly, Ewing's sarcoma and osteosarcoma, the most common primary malignant bone tumors, both tend to undergo recurrent *TP53* mutations (Chen et al., 2014; Tirode et al., 2014).

Taken together, these observations suggest the following model: in a cell governed by the tumor-suppressor p53, RUNX3 is invoked by either DNA damage or oncogenic stress, and positively regulates p53, which protects against MYC. Upon p53 inactivation, however, RUNX3 is unable to properly associate with p53, and therefore begins to act as an oncogene by aberrantly activating MYC (Fig. 1).

Previously, we reported that RUNX3 prevents tumorigenesis of the gastrointestinal tract, possibly by repressing MYC. This may appear to contradict our proposal that MYC is activated by RUNX3. In mechanistic terms, RUNX3 attenuates the DNA-binding activity of the TCF4/β-catenin complex that induces MYC, the principal oncogene for gastrointestinal cancer (Ito et al., 2008; Ito et al., 2011). It should be noted, however, that this tumor-suppressive role of RUNX3 was demonstrated in precancerous states using systemic *Runx3*-decifient mouse lines, without reference to p53 status *in vivo*. It remains to be determined whether RUNX3 continues to function as a tumor-suppressor by repressing MYC

even after p53 is inactivated.

CONCLUSIONS AND PERSPECTIVES

We proposed p53 status as a contextual determinant of the dual nature of RUNX3. In this model, p53 inactivation is the crucial event responsible for causing RUNX3 to contribute to cancer development. If that is the case, p53 deficiency and MYC dysregulation, two major phenomena related to most cancer initiation and progression in humans, may be connected by RUNX3, providing a rationale for targeting RUNX3 in malignancies (Fig. 2).

Indeed, Runx3 evidently does help to repress tumorigenesis in mouse models of gastrointestinal and lung cancers, but the *p53* status of these tumors has not been considered. Validation of our hypothesis will require more sophisticated mouse models in which *Runx3* or *p53* are disrupted in a tissue-specific or temporally specific manner. Also, the genomic elements responsible for upregulation of Myc by Runx3, such as *N-Me*, should be studied further. In particular, it should be determined whether depletion of a specific element, such as a specific RUNX binding site, would suppress tumorigenesis in animal cancer models.

In fact, several other transcription factors play dual roles in cancer development: NF-κB in TNF-α signaling (Perkins, 2004); SMADs in TGF-β signaling (David and Massagué, 2018); AP-1 in MAPK signaling (Eferl and Wagner, 2003); YAP/TAZ in Hippo signaling (Moroishi et al., 2015); and RBPJ in Notch signaling (Lobry et al., 2014). Many of these signal-driven transcription factors (SDTFs) (Zhang and Glass, 2013) interact with RUNX3 (Chuang et al., 2013). RUNX family members are thought to be lineage-determining transcription factors (LDTFs) that specify cell identity and determine the genome-wide binding pattern of SDTFs over the course of normal development (Link et al., 2018; Zhang and Glass, 2013). Thus, a contextual determinant of the dual nature of RUNX3 might be shared by other transcription factors.

Disclosure

The authors have no potential conflicts of interest to disclose.

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