Minireview

Oncogenic RUNX3: A Link between p53 Deficiency and MYC Dysregulation

Yuki Date¹,² and Kosei Ito¹,*

¹Department of Molecular Bone Biology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8588, Japan, ²Japan Society for the Promotion of Science, Tokyo 102-0083, Japan
*Correspondence: itok@nagasaki-u.ac.jp
https://doi.org/10.14348/molcells.2019.0285
www.molcells.org

INTRODUCTION

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
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<sup>G12D</sup>–Runx3<sup>p14ARF<sub>−/−</sub></sup>–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-Ubrela 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<sup>R175H</sup> (p53<sup>R172H</sup> 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<sup>R175H</sup> is also capable of directly interacting with RUNX3, and that the p53<sup>R175H</sup>–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<sup>R175H</sup> 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).

---

**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                        | (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)      |
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 RBPI 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 CBP 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 p16ink, 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-deficient 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 TNFα 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 RBPs 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.

**ORCID**

Yuki Date https://orcid.org/0000-0002-7357-000X
Kosei Ito https://orcid.org/0000-0002-8416-2466

**REFERENCES**

Adorno, M., Cordenonsi, M., Montagner, M., Dupont, S., Wong, C., Hann, B., Solari, A., Bobisse, S., Rondina, M.B., Guzzardo, V., et al. (2009). A Mutant-p53/Smad complex opposes p63 to empower TGFbeta-induced metastasis. Cell 137, 87-98.

Bae, S.C., Koljivadi, A.M., and Ito, Y. (2019). Functional relationship between p53 and RUNX proteins. J. Mol. Cell Biol. 11, 224-230.

Barghout, S.H., Zepeda, N., Vincent, K., Azad, A.K., Xu, Z., Yang, C., Steed, H., Postovit, L.M., and Fu, Y. (2015). RUNX3 contributes to carboplatin resistance in ovarian carcinoma cancer cells. Gynecol. Oncol. 138, 647-655.

Bauer, O., Sharir, A., Kimura, A., Hantisteanu, S., Takeda, S., and Groner, Y. (2015). Loss of osteoblast Runx3 produces severe congenital osteopenia. Mol. Cell. Biol. 35, 1097-1109.

Belver, L. and Ferrando, A. (2016). The genetics and mechanisms of T cell acute lymphoblastic leukaemia. Nat. Rev. Cancer 16, 494-507.

Bledsoe, K.L., McGee-Lawrence, M.E., Camilleri, E.T., Wang, X., Riester, S.M., van Wijnen, A.J., Oliveira, A.M., and Westendorf, J.J. (2014). RUNX3 facilitates growth of Ewing sarcoma cells. J. Cell. Physiol. 229, 2049-2056.

Blyth, K., Terry, A., Mackay, N., Vaillant, F., Bell, M., Cameron, E.R., Neil, J.C., and Stewart, M. (2001). Runx2: a novel oncogenic effector revealed by in vivo complementation and retroviral tagging. Oncogene 20, 295-302.

Blyth, K., Terry, A., O’Hara, M., Baxter, E.W., Campbell, M., Stewart, M., Donehower, L.A., Onions, D.E., Neil, J.C., and Cameron, E.R. (1999). Synergy between a human c-myc transgene and p53 null genotype in murine thymic lymphomas: contrasting effects of homozygous and heterozygous p53 loss. Oncogene 20, 1717-1723.

Bushweller, J.H. (2019). Targeting transcription factors in cancer - from undruggable to reality. Nat. Rev. Cancer 19, 611-624.

Chang, T.L., Ito, K., Ko, T.K., Liu, Q., Salto-Tellez, M., Yeoh, K.G., Fukamachi, H., and Ito, Y. (2010). Claudin-1 has tumor suppressive activity and is a direct target of RUNX3 in gastric epithelial cells. Gastroenterology 138, 255-265.

Chen, X., Bahrami, A., Pappo, A., Easton, J., Dalton, J., Hedlund, E., Ellison, D., Shurtleff, S., Wu, G., Wei, L., et al. (2014). Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. Cell Rep. 7, 104-112.

Chen, H., Crosley, P., Azad, A.K., Gupta, N., Gokul, N., Xu, Z., Weinfeld, M., Postovit, L.M., Pangas, S.A., Hitt, M.M., et al. (2019). RUNX3 promotes the tumorigenic phenotype in KGN, a human granulosa cell tumor-derived cell line. Int. J. Mol. Sci. 20, E4371.

Chuang, L.S., Ito, K., and Ito, Y. (2017). Roles of RUNX in solid tumors. Adv. Exp. Med. Biol. 962, 299-320.

Chuang, L.S.H., Ito, K., and Ito, Y. (2013). RUNX family: regulation and diversification of roles through interacting proteins. Int. J. Cancer 132, 1260-1271.

Chi, X.Z., Yang, J.O., Lee, K.Y., Ito, K., Sakakura, C., Li, Q.L., Kim, H.R., Cha, E.J., Lee, Y.H., Kaneda, A., et al. (2005). RUNX3 suppresses gastric epithelial cell growth by inducing p21(WAF1/Cip1) expression in cooperation with p53. J. Biol. Chem. 280, 807-810.

Choi, A., Illendula, A., Pulikkan, I.A., Roderick, J.E., Tesell, J., Yu, J., Herrmann, N., Zhu, L.J., Castilla, L.H., Bushweller, J.H. (2019). Targeting transcription factors in cancer - from undruggable to reality. Nat. Rev. Cancer 19, 611-624.

Cunningham, L., Finnckbeiner, S., Hyde, R.K., Southall, N., Marugan, J., Yedavalli, VR.K., Dehdsahi, S.J., Reinhold, W.C., Alemu, L., Zhao, L., et al. (2012). Identification of benzodiazepine Ro5-3335 as an inhibitor of CBF1-CBP interaction. Proc. Natl. Acad. Sci. U.S.A. 109, 14592-14597.

Damdinsuren, A., Matsushita, H., Ito, M., Tanaka, M., Jin, G., Tsukamoto, H., Asai, S., Ando, K., and Miyachi, H. (2015). FLT3-ITD drives Ara-C resistance in leukemic cells via the induction of RUNX3. Leuk. Res. 39, 1405-1413.

David, C.J. and Massagué, J. (2018). Contextual determinants of TGFβ action in development, immunity and cancer. Nat. Rev. Mol. Cell Biol. 19, 419-435.

Donehower, L.A. and Lozano, G. (2009). 20 years studying p53 functions in genetically engineered mice. Nat. Rev. Cancer 9, 831-841.

Eferl, R. and Wagner, E.F. (2003). AP-1: a double-edged sword in tumorigenesis. Nat. Rev Cancer 3, 859-868.

Eischen, C.M., Weber, J.D., Roussel, M.F., Sherr, C.J., and Cleveland, J.L. (1999). Disruption of the ARF-Mdm2-p53 tumor suppressor pathway in Myc-induced lymphomagenesis. Genes Dev. 13, 2658-2669.

Hay, J., Gilroy, K., Huser, C., Kilbey, A., McDonald, A., MacCallum, A., Holroyd, A., Cameron, E., and Neil, J.C. (2019). Collaboration of MYC and
RUN2 in lymphoma simulates T-cell receptor signaling and attenuates p53 pathway activity. J. Cell. Biochem. 120, 18332-18345.

He, L, He, X, Lim, L.P, de Stanchina, E., Xuan, Z., Liang, Y., Yue, W, Zender, L, Magnus, J., Ridzon, D., et al. (2007). A microRNA component of the p53 tumour suppressor network. Nature 447, 1130-1134.

He, Y, de Castro, L.F., Shin, M.H., Dubois, W, Yang, H.H., Jiang, S., Mishra, P.J, Ren, L, Gou, H, Lal, A, et al. (2015). p53 Loss increases the osteogenic differentiation of bone marrow stromal cells. Stem Cells 33, 1304-1319.

Herranz, D, Ambesi-Impombato, A, Palomero, T, Schnell, S.A., Belver, L, Wendcor, A.A., Xu, L, Castillo-Martin, M, Llovet-Navás, D, Cordon-Cardo, C, et al. (2014). A NOTCH1-driven MYC enhancer promotes T cell development, transformation and acute lymphoblastic leukemia. Nat. Med. 20, 1130-1137.

Ho, J.S.L, Ma, W, Mao, D.Y.L, and Benchimol, S. (2005). p53-Dependent transcriptional repression of c-myc is required for G1 cell cycle arrest. Mol. Cell. Biol. 25, 7423-7431.

Ikushima, H, and Miyazono K. (2010). TGFbeta signalling: a complex web in cancer progression. Nat. Rev. Cancer 10, 415-424.

Ito, K, Chuang, L.S.H, Ito, T, Chang, T.L, Fukamachi, H, Salto-Tellez, M, and Ito, Y. (2011). Loss of Runx3 is a key event in inducing precancerous state of the stomach. Gastroenterology 140, 1536-1546.

Ito, K, Lim, A.C.B, Salto-Tellez, M, Motoda, L, Osato, M, Chuang, L.S.H, Lee, C.W.L, Voon, D.C.C, Koo, J.K.W, Wang, H, et al. (2008). RUNX3 attenuates β-catenin/T cell factors in intestinal tumorigenesis. Cancer Cell 14, 226-237.

Ito, Y, Bae, S.C, and Chuang, L.S.H. (2015). The RUNX family: development-metabolic regulators in cancer. Nat. Rev. Cancer 15, 81-95.

Kubota, S, Tokunaga, K, Umezoe, T, Yokomizo-Nakano, T, Sun, Y, Oshima, M, Tan, K.T, Yang, H, Kanai, A, Iwanaga, E, et al. (2019). Lineage-specific RUNX2 super-enhancer activates MYC and promotes the development of blast plasmacytoid dendritic cell neoplasm. Nat. Commun. 10, 1653.

Lee, C.W, Chuang, L.S, Kimura, S, Lai, S.K, Ong, C.W, Yan, B, Salto-Tellez, M, Choollani, M, and Ito, Y. (2011b). RUNX3 functions as an oncogene in ovarian cancer. Gynecol. Oncol. 122, 410-417.

Lee, J.H, Pyon, J.K, Kim, D.W, Lee, S.H, Nam, H.S, Kang, S.G, Kim, C.H, Lee, Y.J, Chun, J.S, and Cho, M.K. (2011a). Expression of RUNX3 in skin cancers. Clin. Exp. Dermatol. 36, 769-774.

Lee, J.W, Kim, D.M, Jang, J.W, Park, T.G, Song, S.H, Lee, Y.S, Chi, X.Z, Park, I.Y, Hyun, J.W, Ito, Y, et al. (2019). RUNX3 regulates cell cycle-dependent chromatin dynamics by functioning as a pioneer factor of the restriction-point. Nat. Commun. 10, 1897.

Lee, J.W, Van wijnen, A, and Bae, S.C. (2017). RUNX3 and p53: how two tumor suppressors cooperate against oncogenic Ras? Adv. Exp. Med. Biol. 962, 321-332.

Lee, Y.S, Lee, J.W, Jang, J.W, Chi, X.Z, Kim, J.H, Li, Y.H, Kim, M.K, Kim, D.M, Choi, B.S, Kim, E.G, et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. Cancer Cell 24, 603-616.

Lengner, C.J, Steinman, H.A, Gagnon, J, Smith, T.W, Henderson, J.E, Kream, B.E, Stein, G.S, Lian, J.B, and Jones, S.N. (2006). Osteoblast differentiation and skeletal development are regulated by Mdm2-p53 signaling: switching an oncogene to a tumor suppressor. Blood 123, 2451-2459.

Ma, X, Liu, Y, Liu, Y, Alexandrov, L.B, Edmonson, M.N, Gawad, C, Zhou, X, Li, Y, Rusch, M.C, Easton, J, et al. (2018). Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. Nature 555, 371-376.

Martins, C.P, Brown Swigart, L, and Evan, G.I. (2006). Modeling the therapeutic efficacy of p53 restoration in tumors. Cell 127, 1323-1334.

Morita, K, Suzuki, K, Maeda, S, Matsuo, A, Mitsuda, Y, Tokushige, C, Kashiwazaki, G, Taniguchi, J, Maeda, R, Noura, M, et al. (2017). Genetic regulation of the RUNX transcription factor family has antitumor effects. J. Clin. Invest. 127, 2815-2828.

Moroishi, T, Hansen, C.G, and Guan, K.L. (2015). The emerging roles of YAP and TAZ in cancer. Nat. Rev. Cancer 15, 73-79.

Murphy, D.J, Juntila, M.R, Pouyet, L, Kamezis, A, Shchors, K, Bui, D.A, Brown Swigart, L, Johnson, L, and Evan, G.I. (2008). Distinct thresholds govern Myc's biological output in vivo. Cancer Cell 14, 447-457.

Neil, J.C, Gilroy, K, Borland, G, Hay, J, Terry, A, and Kilbey, A. (2017). The RUNX genes as conditional oncogenes: insights from retroviral targeting and mouse models. Adv. Exp. Med. Biol. 962, 247-264.

Nevadunksy, N.S, Barbieri, J.S, Kwong, J, Merritt, M.A, Welch, W.R, Berkowitz, R.S, and Mok, S.C. (2009). RUNX3 protein is overexpressed in human epithelial ovarian cancer. Gynecol. Oncol. 112, 325-330.

Okada, N, Lin, C.P, Ribeiro, M.C, Biton, A, Lai, G, He, X, Bu, P, Vogel, H, Jablons, D.M, Keller, A.C, et al. (2014). A positive feedback between p53 and miR-34 miRNAs mediates tumor suppression. Genes Dev. 28, 438-450.

O’Shea, D, O’Riain, C, Taylor, C, Waters, R, Carlotti, E, MacDougall, F, Gribben, J, Rosenwald, A, Ott, G, Rimsha, L.M, et al. (2008). The presence of TP53 mutation at diagnosis of follicular lymphoma identifies a high-risk group of patients with shortened time to disease progression and poorer overall survival. Blood 112, 3126-3129.

Ozaki, T, Nakagawara, A, and Nagase, H. (2013). RUNX family participates in the regulation of p53-dependent DNA damage response. Int. J. Genomics 2013, 271347.

Perkins, N.D. (2004). NF-kappaB: tumor promoter or suppressor? Trends Cell. Biol. 14, 64-69.

Phesse, T.J, Myant, K.B, Cole, A.M, Ridgway, R.A, Pearson, H, Muncan, van den Brink, G.R, Voudsen, K.H, Sears, R, Vassilev, L.T, et al. (2014). Endogenous c-Myc is essential for p53-induced apoptosis in response to DNA damage in vivo. Cell Death Differ. 21, 956-966.

Porter, J.R, Fisher, B.E, Baranello, L, Liu, J.C, Kambach, D.M, Nie, Z, Koh, W.S, Luo, J, Stommel, J.M, Levins, D, et al. (2017). Global inhibition with specific activation: how p53 and MYC redistribute the transcriptome in the DNA double-strand break response. Mol. Cell 67, 1013-1025.

Pulikkan, J., O’Hagan, K., O’Riain, C., Taylor, C., Waters, R., Carlotti, E., MacDougall, F., Gribben, J., Rosenwald, A., Ott, G., Rimsha, L.M., et al. (2008). The presence of TP53 mutation at diagnosis of follicular lymphoma identifies a high-risk group of patients with shortened time to disease progression and poorer overall survival. Blood 112, 3126-3129.

Rodriguez-Ubrea, J, Ciudad, L, van Oevelen, C, Parrá, M, Graf, T, and Ballestar, E. (2014). C/EBPα-mediated activation of microRNAs 34a and 223 inhibits Lef1 expression to achieve efficient reprogramming into macrophages. Mol. Cell. Biol. 34, 1145-1157.

Sachdeva, M, Zhu, S, Wu, F, Wu, H, Walia, V, Kumar, S, Elble, R, Watabe, K, and Mo, Y.Y. (2009). p53 Represses c-Myc through induction of the tumor suppressor miR-145. Proc. Natl. Acad. Sci. U. S. A. 106, 3207-3212.

Schmitt, C.A, McCurrach, M.E, de Stanchina, E, Wallace-Brodeur, R.R, and Lowe, S.W. (1999). INK4a/ARF mutations accelerate lymphomagenesis and promote chemoresistance by disabling p53. Genes Dev. 13, 2670-2677.
Ham, M.F., Salto-Tellez, M., Shimizu, N., et al. (2017). RUNX3 is oncogenic in natural killer/T-cell lymphoma and is transcriptionally regulated by MYC. Leukemia 31, 2219-2227.

Sherr, C.J. (2006). Divorcing ARF and p53: an unsettled case. Nat. Rev. Cancer 6, 663-673.

Shi, J., Whyte, W.A., Zepeda-Mendoza, C.J., Milazzo, J.P., Shen, C., Roe, J.S., Minder, J.L., Mercan, F., Wang, E., Eckersley-Maslin, M.A., et al. (2013). Role of SWI/SNF in acute leukemia maintenance and enhancer-mediated Myc regulation. Genes Dev. 27, 2648-2662.

Shimizu, K., Yamagata, K., Kurokawa, M., Mizutani, S., Tsunematsu, Y., and Kitabayashi, I. (2013). Roles of AML1/RUNX1 in T-cell malignancy induced by loss of p53. Cancer Sci. 104, 1033-1038.

Shin, M.H., He, Y., Marrogi, E., Pipierdi, S., Ren, L., Khanna, C., Gorlick, R., Liu, C., and Huang, J. (2016). A RUNX2-mediated epigenetic regulation of the survival of p53 defective cancer cells. PLoS Genet. 12, e1005884.

Tirode, F., Surdez, D., Ma, X., Parker, M., Le Deley, M.C., Bahrami, A., Zhang, Z., Lapouble, E., Grossetête-Lalami, S., Rusch, M., et al. (2014). Genomic landscape of Ewing sarcoma defines an aggressive subtype with co-association of STAG2 and TP53 mutations. Cancer Discov. 4, 1342-1353.

Tsunematsu, T., Kudo, Y., Izuoka, S., Ogawa, I., Fujita, T., Kurihara, H., Abiko, Y., and Takata, T. (2009). RUNX3 has an oncogenic role in head and neck cancer. PLoS One 4, e5892.

den Deen, M., Taipaleenmäki, H., Zhang, Y., Teplyuk, N.M., Gupta, A., Cinghu, S., Shogren, K., Maran, A., Yaszemski, M.J., Ling, L., et al. (2013). MicroRNA-34c inversely couples the biological functions of the runt-related transcription factor RUNX2 and the tumor suppressor p53 in osteosarcoma. J Biol. Chem. 288, 21307-21319.

Whittle, M.C. and Hingorani, S.R. (2017). Runx3 and cell fate decisions in pancreas cancer. Adv. Exp. Med. Biol. 962, 333-352.

Whittle, M.C., Izerađine, K., Rani, PG., Feng, L., Carlson, M.A., DelGiorno, K.E., Wood, L.D., Goggins, M., Hruban, R.H., Chang, A.E., et al. (2015). RUNX3 controls a metastatic switch in pancreatic ductal adenocarcinoma. Cell 161, 1345-1360.

Wotton, S.F., Blyth, K., Kilbey, A., Jenkins, A., Terry, A., Bernardin-Fried, F., Friedman, A.D., Baxter, E.W., Neil, J.C., and Cameron, E.R. (2004). RUNX1 transformation of primary embryonic fibroblasts is revealed in the absence of p53. Oncogene 23, 5476-5486.

Yamada, C., Ozaki, T., Ando, K., Suenaga, Y., Inoue, K.I., Ito, Y., Okoshi, R., Kageyama, H., Kimura, H., Miyazaki, M., et al. (2010). RUNX3 modulates DNA damage-mediated phosphorylation of tumor suppressor p53 at Ser-15 and acts as a co-activator for p53. J. Biol. Chem. 285, 16693-16703.

Yano, T., Ito, K., Fukamachi, H., Chi, X.Z., Wee, H.J., Inoue, K.I., Ida, H., Bouillet, P., Strasser, A., Bae, S.C., et al. (2006). The RUNX3 tumor suppressor upregulates Bim in gastric epithelial cells undergoing transforming growth factor beta-induced apoptosis. Mol. Cell. Biol. 26, 4474-4488.

Yoshida, C.A., Yamamoto, H., Fujita, T., Furuiuchi, T., Ito, K., Inoue, K.I., Yamana, K., Zanma, A., Takada, K., Ito, Y., et al. (2004). Runx2 and Runx3 are essential for chondrocyte maturation, and Runx2 regulates limb growth through induction of Indian hedgehog. Genes Dev. 18, 952-963.

Young, K.H., Leroy, K., Møller, M.B., Colleoni, G.W.B., Sanchez-Beato, M., Kerbauy, F.R., Haicoun, C., Eickhoff, J.C., Young, A.H., Gaulard, P., et al. (2008). Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood 112, 3088-3098.

Zhang, D.X. and Glass, C.K. (2013). Towards an understanding of cell-specific functions of signal-dependent transcription factors. J. Mol. Endocrinol. 51, T37-T50.

Zindy, F., Eschen, C.M., Randle, D.H., Kamijo, T., Cleveland, JL., Sherr, C.J., and Roussell, M.F. (1998). Myc signaling via the ARF tumor suppressor regulates p53-dependent apoptosis and immortalization. Genes Dev. 12, 2424-2433.

Oncogenic RUNX3 between p53 Deficiency and MYC Dysregulation

Yuki Date & Kosei Ito