Molecules and Cells

Overview

Tour d'Horizon of Recent Advances in RUNX Family Gene Research

Suk-Chul Bae*

Department of Biochemistry, College of Medicine, Chungbuk National University, Cheongju 28644, Korea
*Correspondence: scbae@chungbuk.ac.kr
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www.molcells.org

RUNX family transcription factors are essential regulators of diverse developmental processes, including cell proliferation, differentiation, apoptosis, and cell lineage specification (Ito et al., 2015). *RUNX* genes were independently identified as the fly segmentation gene Runt, a leukemia associated gene, and the subunit of a virus enhancer binding protein. Mammals possess three *RUNX* genes, *RUNX1*, *RUNX2*, and *RUNX3*, which form a heterodimeric complex in the presence of a β subunit, CBFβ. Although these *RUNX* family members bind to the same nucleotide sequence (PuACCPuCA/TGPyGGT-Py), each member has distinct tissue-specific roles (Ito et al., 2015). All are deregulated in one way or another in human diseases, indicating they are intimately involved in the pathogenesis of human disease. This special issue describes the roles of *RUNX* proteins in developmental processes and tumorigenesis.

The regulatory function of *RUNX1* in hematopoiesis was first revealed when Runx1 was disrupted in mice (Okuda et al., 1996). *RUNX1* gene disruptions caused by chromosomal translocations and mutations are frequently detected in hematological diseases, such as acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) (Bellissimo and Speck, 2017), indicating that *RUNX1* is intimately involved in hematopoiesis and hematopoietic lineage specification and its functional dysregulation is associated with leukemia. More recent studies show that *RUNX1* is also associated with various solid tumors.

The regulatory function of *RUNX2* in osteogenesis was first revealed when Runx2 was disrupted in mice (Komori et al., 1997; Otto et al., 1997). Based on these studies, further work showed that human autosomal dominant bone disease cleidocranial dysplasia (CCD) is caused by *RUNX2* haploinsufficiency (Lee et al., 1997; Mundlos et al., 1997; Otto et al., 1997), establishing Runx2 as a master regulator of osteogenesis. Overexpression of *RUNX2* occurs in various solid tumors including osteosarcoma, lymphoma, and breast cancer, indicating that functional dysregulation of *RUNX2* is associated with tumorigenesis (Blyth et al., 2006; Ferrari et al., 2013; Sadikovic et al., 2010).

Runx3 knockout mice, the result of a collaboration between my laboratory and that of Yoshiaki Ito (Li et al., 2002), cancer cell lines, and surgically dissected cancer tissues revealed that loss of *RUNX3* expression occurs in, and is causally related to, gastric cancer (Li et al., 2002). *RUNX3* inactivation in gastric cancer is the combined result of its hemizygous deletion and silencing by DNA hypermethylation (Li et al., 2002). Silencing of *RUNX3* by DNA hypermethylation was also observed in various other cancers, suggesting that *RUNX3* functions as a tumor suppressor (Ito et al., 2015). Subsequent studies revealed that *RUNX3* plays key roles in suppressing not only gastric cancer but also lung cancer (Lee et al., 2013). *RUNX3* also functions as an oncogene is some cancers. For example, *RUNX3* is overexpressed in head and neck cancer, squamous cell carcinoma (SCC), epithelial ovarian cancer, and basal cell carcinoma (Lee et al., 2011; Salto-Tellez et al., 2006; Tsunematsu et al., 2009). In pancreatic cancer, *RUNX3* functions as a tumor suppressor at the early stage and as an oncogene at the late stage of tumor

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progression (Whittle et al., 2015). These opposing roles of *RUNX3* can be reconciled by the recent observation that *RUNX3* is important for context-dependent cell fate decisions at the G1 restriction point, i.e., it determines whether cells progress through the cell cycle or enter apoptosis (Lee et al., 2019a). Therefore, *RUNX3* overexpression has the potential to disturb restriction point regulation and cause unprogrammed cell proliferation in some tissues.

RUNX family members have both tumor suppressive and oncogenic activity. What makes *RUNX* a tumor suppressor or an oncogene? This question can only be answered after we know more about how cancers develop and how *RUNX* genes determine cell fate, which is critical for regulating developmental processes in diverse tissues. In this regard, it is worth mentioning that restriction point regulation, which is critical in deciding whether cells proliferate, differentiate and undergo apoptosis, is disrupted in nearly all cancer cells. Recently, all three *RUNX* family members were shown to be involved in restriction point regulation (Lee et al., 2019a; 2019b). It is worth emphasizing that *RUNX* family members bind to the same nucleotide sequence. Therefore, the results of all these studies suggest that the diverse roles of *RUNX* family members can be explained, at least partly, by their participation in a common cell fate decision mechanism that makes cell type-specific and context-dependent decisions.

Disclosure

The author has no potential conflicts of interest to disclose.

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ORCID

Suk-Chul Bae https://orcid.org/0000-0002-4613-3517

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