FBXO22, an epigenetic multiplayer coordinating senescence, hormone signaling, and metastasis

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INTRODUCTION

F-box proteins contain at least one F-box domain, a motif consisting of approximately 50 amino acids, through which F-box proteins bind to SCF ubiquitin ligase complexes. The SCF complex is composed of S-phase kinase-associated protein 1 (SKP1), RING of cullin 1 (ROC1; also called RBX1), Cullin 1 (CUL1), and variable F-box proteins that determine substrate specificity. F-box proteins are divided into 3 subclasses depending on the presence of specific substrate recognition domains, such as Fbxw which contains WD40 repeat domains, Fbxl which contains leucine-rich repeat, and Fbxo which contains various domains that are not fully characterized. Thirty-seven F-box proteins have been identified to date, and their roles in various cellular processes are emerging.
proteins were designated as F-box only (Fbxo) proteins within putative F-box proteins in the human genome. In most cases, Fbxo proteins contain the F-box domain in their N-terminus and various types of protein interaction domains in their C-terminus, the latter of which mediate substrate bindings. Recently, several lines of studies have begun to uncover some interesting physiological functions of Fbxo proteins, which are attributed to uncharacterized protein interaction domains. For example, FBXO22 has been reported to be involved in tumorigenesis, metastasis, and senescence. In this review, we focus on our discussion on the recent biochemical and biomedical evidence showing the tumor suppressor or oncogenic roles for FBXO22.

2 FBXO22 IS CRITICAL FOR INDUCTION OF SENESCENCE-ASSOCIATED PHENOTYPES

Cellular senescence was first discovered as the inability of cultured human cells to proliferate indefinitely. Later on, several lines of evidence revealed that senescence was also triggered by diverse genotoxic stimuli including telomere dysfunction, activated oncogenes, reactive oxygen species, and DNA damage. Senescence is now believed to play a critical role in the suppression of tumorigenesis as well as geriatric changes in various organs due to its inherent nature to permanently cease cell proliferation. Thus, one important hallmark of senescence is the inability of cells to proliferate in response to any physiological mitotic stimuli. Induction of cellular senescence requires functional p53 and pRB family proteins, which frequently undergo oncogenic mutations in a majority of human cancers. These notions are strongly supported by the fact that cellular senescence is bypassed by viral oncoproteins inhibiting either p53 or pRB family proteins. However, the precise roles of these tumor suppressors in the process of senescence were incompletely understood. We have uncovered the molecular mechanisms of permanent cell cycle arrest in which p53 activation at G2 phase plays an essential role in the senescence process. Thus, these observations strongly suggest that pathways or proteins regulating the amount and the timing of p53 activation upon senescent inducing stimuli are the key factors for senescence regulation.

Another hallmark of senescence is senescence-associated secretory phenotypes (SASP), a robust secretion of numerous growth factors, cytokines, proteases, and other proteins. Such effects support various pathophysiological phenotypes in age-related diseases, such as chronic inflammation, disruption of tissue architecture, and growth stimulation. The permanent cessation of cell proliferation and SASP are considered 2 hallmarks of senescence and are often coordinately induced. However, their mechanisms do not always overlap. For example, p38MAPK is critically required for SASP, but activated p33 restrains function of p38MAPK. Thus, there appear to be some missing links that more clearly explain the antagonistic effects of p53 on the induction of the 2 representative hallmarks of senescence.

To address the above issues, we first tried to identify genes that are predominantly expressed in senescent cells, and whose product could regulate the activity of p53. Global gene expression analysis revealed that FBXO22 was markedly induced in senescent cells. Interestingly, FBXO22 is upregulated at the late phase of the senescent process in a p53-dependent manner. ChIP-seq analysis confirmed that p53 was recruited to the transcription start site of the FBXO22 gene upon genotoxic stress. Although activation of p53 is critically required for the induction of senescence, it should be downregulated at the late phase of the senescent process for SASP induction. We found that FBXO22 is essential for this downregulation of p53. SCF<sub>FBXO22</sub> specifically ubiquitylates methylated p53 complexed with KDM4A for degradation at the late phase of senescence. FBXO22 binds to p53 and KDM4A through its FIST-N and FIST-C domains, respectively. Formation of a ternary complex between FBXO22, methylated p53, and KDM4A facilitates ubiquitylation of p53 by SCF complexes. In this case, KDM4A is likely to act as a scaffold independent of its demethylase activity. Importantly, downregulation of methylated p53 by SCF<sub>FBXO22</sub> is required for the induction of p16 and SASP, the former of which is critical for permanent cessation of cell proliferation upon any mitogen stimuli (Figure 1). SCF<sub>FBXO22</sub> as a ubiquitin ligase for p53 is confirmed by in vivo experiments showing marked accumulation of p53 in all organs tested from FBXO22 knockout mice. Taken together, the results suggest that FBXO22 serves as a key regulator of senescence induction through the creation of a negative feedback loop with p53. Formation of this negative feedback loop between p53 and its ubiquitin ligases such as mdm2<sup>25</sup> and FBXO22 might be a common mechanism by which transcriptional activity of p53 could be finely tuned.

3 FBXO22 DETERMINES SENSITIVITY OF BREAST CANCERS TO ENDOCRINE TREATMENT

Approximately 90,000 women are annually affected with breast cancer in Japan. Up to 70% of the cases are estrogen receptor-α (ER)-positive. Human Epidermal Growth Factor Receptor Type 2 (HER2)-negative luminal type breast cancer, that are considered to be relatively non-aggressive and sensitive to hormone therapy. Patients with the luminal breast cancer, especially for pre-menopausal women, are treated with selective estrogen receptor modulators (SERMs) such as tamoxifen (TAM) as standard adjuvant therapy after surgery. However, substantial patients treated with TAM undergo a relapse within 15 years due to de novo resistance or acquired resistance. There exist various mechanisms for the hormone therapy resistance that have been extensively investigated for decades. However, these mechanisms are still insufficient to explain the entire picture of the endocrine resistance.

Estrogen-bound ER regulates transcription of various downstream target genes through the recruitment of coactivators or corepressors. This action is synergized by interplay between transactivation function 1 (AF1) and transactivation function 2.
(AF2). SERMs block estrogen action (agonistic action) in many tissues, but in some tissues, they act like estrogen (agonistic action). This selective modulation has been reported to be regulated by a complete blockade of AF2 function in a context specific manner. Previously, it has been reported that steroid receptor coactivator 3 (SRC-3) and HER2 in breast cancer cells convert SERMs actions from an antagonistic to agonistic. However, given that overexpression of coactivators does not suppress the antagonistic action of SERMs and that some ER-positive breast cancers show a resistance to SERMs independent of HER2, there should be unidentified mechanisms underlying cofactor interactions with ER, modulating SERMs actions.

To identify the factor(s) that determines the antagonistic activity of SERMs, we first tried to uncover the mechanisms underlying regulation of ER signaling and to clarify the complexity of such signaling pathways that are interconnected or that converge into each other. KDM4B is essential for ER-mediated transcription. Therefore, we speculated that the amount of KDM4B complexed with ER might play a key role in cofactor dynamics on ER. ER forms a complex with KDM4B and SRC-3 after estrogen treatment. This complex dissociated after TAM treatment and ER then often formed a complex with N-CoR-HDAC3 repressors. Suppression of proteasome-dependent protein degradation almost completely abrogated these cofactor dynamics on ER. Given that KDM4B depletion dissociated coactivators from estrogen-bound ER, selective degradation of KDM4B complexed with ER might trigger cofactor dynamics on ER.

We then found that FBXO22 regulated the level of KDM4B protein. FBXO22 formed a ternary complex with ER and KDM4B through its FIST-N and FIST-C domains, respectively. Importantly, ER binding to FBXO22 was dependent on the types of ligands. ER predominantly formed a complex with unliganded or SERMs-bound ER, but not E2-bound ER. As the level of KDM4B was drastically decreased by co-expression of FBXO22 and ER, but not by single expression of either one, formation of the ternary complex might facilitate KDM4B ubiquitylation by SCF-FBXO22. Indeed, in vivo ubiquitylation assays under denaturing conditions revealed that SCF-FBXO22 induced ubiquitylation of KDM4B and that this ubiquitylation was enhanced by co-expression of ER in a dose-dependent manner.

Given that proteasomal degradation was a prerequisite for cofactor switching from coactivators to corepressors on ER in response to SERMs treatment, SCF-FBXO22-dependent KDM4B ubiquitylation for degradation might play a critical role in the determination of the antagonistic activity of SERMs. In line with the role of SCF-FBXO22 in the regulation of KDM4B complexed with unliganded or TAM-bound ER, we found that FBXO22 is essential for antagonistic activity of SERMs in ER-positive breast cancer cells. The FBXO22-dependent antagonistic activity of SERMs appeared to be elicited by the AF1 domain of ER. It should be noted that requirement of FBXO22 in antagonistic activity against ER signaling was specific to SERMs, but not to selective ER down-regulators (SERDs), such as fulvestrant.

In agreement with the essential role of FBXO22 in the antagonistic activity of SERMs, mapping of genome-wide ER- and SRC3-binding events by ChIP-Seq analysis revealed that FBXO22 is prerequisite for TAM-mediated SRC-3 release from almost all ER-SRC3-bound genomic regions. In an in vivo xenograft model using NOD-SCID mice, even in the presence of TAM, mice inoculated with T47D cells lacking FBXO22 showed progressive tumor growth, whereas mice inoculated with control T47D cells did not. These
results suggest that FBXO22 is essential for the antagonistic activity of TAM both in vitro and in vivo through selective degradation of KDM4B complexed with unliganded or TAM-bound ER (Figure 2).

In addition to the effect on the sensitivity of breast cancer cells to SERM, FBXO22 deficiency may also contribute to a resistance to aromatase inhibitors, because dissociation of SRC from ER under E2-depleted conditions also requires FBXO22 and degradation of KDM4B. In response to E2-deprivation, SRC was released from ER accompanied by KDM4B degradation in the similar fashion to the response to SERM treatment, whereas N-CoR recruitment was not observed in this case. However, SRC and KDM4B remained attached with ER in cells depleted of FBXO22, and consequently EBAG9 and GREB1, downstream transcriptional target of ER, remained expressed at high level without E2. This supports that FBXO22 physiologically controls shutdown of ER-mediated estrogen signals.

Based on such a critical role of FBXO22 on estrogen signaling, we hypothesized that FBXO22 deficiency may lead to a poor outcome of breast cancer due to a resistance to endocrine therapies. To test this, we performed immunohistochemical analysis of a set of 163 primary ER-positive/HER2-negative T2 breast cancer specimens to determine FBXO22 levels and analyzed its impact on prognosis. Outstandingly, tumors negative for FBXO22 expression showed significantly reduced relapse-free survival (RFS) compared with tumors positive for FBXO22 (Figure 3). This significant difference was not affected by other clinicopathological variants, and preserved in separate cohorts of luminal A–like (low Ki-67), node-negative, grade-1, and tamoxifen-treated tumor cases. Multivariate survival analyses showed that the lack of FBXO22 was independently predictive of a poorer RFS, whereas Ki-67 was not. The association of FBXO22 expression with RFS in ER-positive/HER2-negative breast cancer was further validated in another patient cohort at a different institution.

A biomarker to predict high-risk groups of ER-positive/HER2-negative breast cancer has long been much needed, not only to treat such patients with additional therapy, but also to avoid unnecessary chemotherapy to low-risk patients. Ki-67 may currently represent such a marker. ER-positive/HER2-negative breast cancer has been subclassified as luminal A based on the Ki-67 status to optimize adjuvant therapy. However, a considerable number of patients with low Ki-67 luminal A–like breast cancer experience relapse after adjuvant hormone therapy, thus promoting efforts to seek better predictive markers. To overcome the problem, recent studies focused on multigene panels such as Oncotype DX, MammaPrint, and PAM50. However, these tests require a substantial length of time to come to diagnosis, and high costs. Therefore, FBXO22 immunohistochemical analysis may possibly be a faster and cheaper alternative to the multigene panel tests if its significance on hormone therapy sensitivity is further verified. In that regard, recent analyses of breast cancer prognosis with FBXO22 immunohistochemical analysis further validated its value.

**4 | FBXO22 REGULATES CANCER METASTASES**

Metastases are one of the major causes of cancer-related deaths. Although intense efforts have been made to uncover their underlying mechanisms and identify effective therapeutic targets, progress...
in the treatment of metastatic cancer has been only minimal. Very recently, FBXO22 has been reported to play a key role in the metastatic process of various tumors in vivo. Non-small-cell lung cancers (NSCLC) produce highly metastatic tumors. However, the molecular basis underlying the metastasis of NSCLC is largely unclear. Recent genome-wide analysis showed that a significant portion of metastatic NSCLC associates with mutations in either Keap1 or Nfe2/2, both of which result in the stabilization of Nrf2. Keap1 is a substrate recognition subunit of a Cul3-RING ubiquitin ligase CRL3 complex. Under unperturbed conditions, Keap1-CRL3 constitutively ubiquitylates Nrf2 for proteasome-dependent degradation. Once cells sense oxidative stress, Nrf2 dissociates from Keap1-CRL3 and is consequently stabilized. Transcriptional activity of Nrf2 is then executed by the formation of a heteromeric complex with a Maf on Maf recognition element (MARE). Maf forms a complex with Bach1 to repress MAREs under unperturbed conditions. Upon oxidative stress, increased free heme binds to Bach1 through its heme regulatory motif (HRM), which triggers its proteasomal degradation, promoting the transcriptionally active Nrf2-Maf complex.

In line with the frequent mutations in Keap1 in metastatic NSCLC, loss of Keap1 in mice caused a predisposition to lung adenocarcinoma (KrasL;G12D; p53flox/flox), resulting in an increase in the incidence of metastasis. Lung adenocarcinoma cells lacking Keap1 showed high cell migration in vitro and a metastatic ability in vivo. Gene Set Enrichment Analysis of RNA sequencing using these lung adenocarcinoma cells revealed that loss of Keap1 was associated with the Bach1 signature with the highest enrichment score. Indeed, the level of Bach1 was very high in Keap1-mutated lung adenocarcinoma cells. Most intriguingly, loss of Keap1 led to an accumulation of Bach1 in a Nrf2-induced heme oxygenase-1 (Ho1)-dependent manner. Increased Ho1 promoted degradation of free heme.

Hemin binding of Bach1 is reported to facilitate its ubiquitylation-dependent degradation. Although HOIL-1 is involved in the ubiquitylation of Bach1 in a manner depending on its hemin binding, mass spectrometry analysis has identified FBXO22 as a hemedependent binding protein to Bach1. Indeed, FBXO22 depletion and overexpression results in the promotion of cell migration in vitro and the blockage of Bach1-driven metastasis of lung adenocarcinoma.
respectively. Thus, the results suggest that loss of FBXO22 in lung adenocarcinoma facilitates metastasis (Figure 4).

In addition to lung adenocarcinomas, FBXO22 was also reported to be involved in the metastasis of breast cancers. Oncopogenic epithelial-mesenchymal transition (EMT) is thought to be one of the main mechanisms underlying invasion and metastasis of breast cancers. EMT is regulated by a transcriptional network consisting of SNAIL, SLUG, ZEB1, ZEB2, and TWIST transcription factors. Increased expression of SNAIL is correlated with a high incidence of metastasis and recurrence, and poor prognosis of breast cancers. Activation of SNAIL sufficiently triggers EMT in breast cancers through downregulation of E-cadherin expression, which is a known marker of EMT. Intriguingly, FBXO22 was reported to ubiquitylate SNAIL for degradation. This degradation was dependent on the phosphorylation of SNAIL by GSK3β. In agreement with GSK3β as a negative regulator of EMT, activation of Wnt signaling by suppression of GSK3β is known to induce EMT.

FBXO22 was also reported to be involved in the metastasis of breast cancers through regulating the level of HDM2. HDM2 is a RING-type E3 ubiquitin ligase that target various oncogenic as well as anti-oncogenic factors, such as p53. Besides regulation of p53, HDM2 also functions in tumorigenesis by targeting various proteins. For example, HDM2 was reported to target E-cadherin for ubiquitylation, regulating tumor cell invasiveness. Although the precise mechanism remains unknown, loss of FBXO22 promotes cell migration and invasion of human breast cancer cells in vitro. In line with this notion, using the mouse 4T1 breast tumor model, FBXO22 knock-down facilitates metastasis of breast cancers in vivo. Taken together with the results from multiple metastasis models, it is tempting to suggest that FBXO22 is an essential factor for regulating metastasis and invasion of cancers. Therefore, its activators represent an effective therapeutic strategy for prevention of cancer metastasis.

5 | PERSPECTIVE

Several lines of evidence have suggested that mutation or aberrant expression of E3 ubiquitin ligases drives the initiation and progression of various types of cancers. Recent advances in FBXO22 research have clearly demonstrated that FBXO22 regulates tumorigenesis at multiple levels including initiation, hormone sensitivity, invasion, and metastasis of cancers. In normal cells, FBXO22 is likely to function as an anti-tumor factor because senescence induction, suppression of hormone-independent cell proliferation, and inhibition of cell migration are known to be involved in tumor suppressive mechanisms. Therefore, Fbxo22 might also regulate other anti-tumor pathways, such as inhibition of anchorage-independent growth, angiogenesis, and escape from immune systems. Although mutations or truncations in the FBXO22 gene are rare events in cancers, levels of FBXO22 expression vary even among the same types of cancers. The level of FBXO22 in cancer cells can be utilized as a predictive value for breast cancers, showing that a low level of FBXO22 in tumor tissues predicts a poorer outcome in ER-positive/HER-2-negative breast cancers with high hazard ratios independently of other markers such as Ki-67 and node status. Therefore, it would be of great interest to comprehensively analyze FBXO22 expression in various types of cancers and to clarify the relationship between the level of FBXO22 and patient outcome. Elucidation of mechanisms underlying the regulation of FBXO22 expression and identification of pathways that modulate the function of FBXO22 would also be important.

ACKNOWLEDGMENTS

This work was supported by MEXT/JSPS KAKENHI under Grant Numbers JP19H05740, JP26250027, JP22118003, and JP16K15239, and by AMED under Grant Numbers JP17cm0106122, JP17fk0310111, and JP17gm5010001, as well as by Ono Medical Research Foundation, Princess Takamatsu Cancer Research Fund, and RELAY FOR LIFE JAPAN CANCER SOCIETY (M.N), by MEXT/JSPS KAKENHI under Grant Number 16H06148 (Y.J), and by MEXT/JSPS KAKENHI under Grant Numbers JP26290042, JP24112005, and 17H03585, and by AMED under Grant Numbers JP16ck0106085h0003 (T.O).

CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

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How to cite this article: Johmura Y, Harris AS, Ohta T, Nakanishi M. FBXO22, an epigenetic multiplayer coordinating senescence, hormone signaling, and metastasis. Cancer Sci. 2020;111:2718–2725. https://doi.org/10.1111/cas.14534