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Friends and foes: Our evolving understanding of the link between Fbxw7 and p53 in cancer

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FbXW7 has long been recognized as an important tumor suppressor that can be disrupted by deletion or gene mutation. FBXW7 is the substrate recognition component of an SCF ubiquitin ligase complex that catalyzes the ubiquitin-mediated degradation of oncogenes such as cyclin E1, c-Myc, Mcl-1, Notch1, mTOR and Jun [1]. The loss or mutation of *FBXW7* can lead to the activation of one or several of these pathways in cancers. Prior examination of tissue specific mouse knockout models of *Fbxw7* has shown that *Fbxw7* loss initiates neoplastic changes associated with uterine carcinosarcomas [2], lymphomas, and liver cancer [3], but *Fbxw7* loss does not invariably lead to tumorigenesis in animal models [4]. The effect of *Fbxw7* loss had not been investigated in models of breast cancer, which is an important question as breast cancer has a high rate of *Fbxw7* deletion and reduced expression associated with promoter methylation [1]. In their new report, Meyer et al. [5] provide clear evidence that *Fbxw7* loss in the mouse mammary gland alters mammary gland biology and can instigate tumor development.

In the $Fbxw7^{fl/fl}$;LGB Cre + pregnancy triggered model of Meyer et al., *Fbxw7* loss leads to high proliferation of mammary epithelial cells, lactation and involution defects [5]. These changes parallel the high proliferation and involution defects that are observed with overexpression of an Fbxw7-refractory form of cyclin E1 within the mammary gland [6]. Tumors then eventuate in $Fbxw7^{-/-}$ animals with a latency of 13–286 days. Meyer et al. found that c-Myc and cyclin E1 regulated pathways were highly engaged in $Fbxw7^{-/-}$ mammary cancers, whereas other pathways downstream of Fbxw7, such as c-Jun and Notch1, were not significantly disrupted. Consequently it appears that the loss of *Fbxw7* in the mammary gland sets a course for tumor development which engages the c-Myc and cyclin E1 pathways, including E2F activation. This is consistent with the molecular profile of these tumors: they are estrogen receptor positive and luminal-like, and luminal subtypes of breast cancer are typified by E2F and Myc signatures [7].

An important observation arising from this study is that *Trp53* loss of function mutations accumulate in mammary tumors following *Fbxw7* loss. Critically, Meyer et al. also document the co-occurrence of *FBXW7* disruption and *TP53* mutation in breast cancer datasets. The co-occurrence of *FBXW7* loss and *TP53* mutation has also been observed in gastric cancer [8] and high grade serous ovarian cancer [9]. In parallel to these studies, several recent investigations have revealed that FBXW7 targets p53 for ubiquitin mediated degradation, and the loss or mutation of *FBXW7* can lead to increased p53 stability and activity [10–12]. The dual effects of *FBXW7* loss to increase p53 stability but also induce *TP53* mutation may seem paradoxical, but it carries a certain logic when considering the temporal development of cancers (Fig. 1). It is possible that an early loss of *FBXW7* in tumorigenesis may be tempered by an increase in p53 stability and function. This would protect cells from chromosomal instability associated with the stabilization of other FBXW7 target proteins such as cyclin E1 [4,13]. In order to continue tumor development the mutation of *TP53* is then a logical next hit to overcome the protective effects of increased p53 (Fig. 1). Of note, Meyer et al. saw two of three tumors had increased p53 expression. p53 was not generally elevated immediately following *Fbxw7* deletion in non-tumor tissue (data not shown in [5]), but the effects of *Fbxw7* depletion on p53 stability are best observed in the context of DNA damage [11,12].

FBXW7 loss and *TP53* mutation represent two common alterations in cancer, and together are likely to represent a formidable driver of cancer development. In support of this, several studies indicate that these two alterations co-operate to augment tumorigenesis [4,13], and the combination of these defects is associated with poorer survival in gastric cancer [8]. Some important questions are still to be answered. Does *FBXW7* loss predispose to activating *TP53* mutations, or mainly to *TP53* loss of function mutations? Meyer et al. identified only loss of function *Trp53* mutations in the $Fbxw7^{-/-}$ mammary gland model. In the context of mammary cancers, *TP53* mutation co-occurred with activation of cyclin E1 and c-Myc pathways, but does *TP53* mutation co-occur with other Fbxw7 activated pathways, such as Notch, Mcl-1 and c-Jun pathways? The answers to both these questions may be dictated by the type of malignancy, as different cancers can rely upon distinct oncogenic pathways. Further studies in this area will be essential to identify the best way to treat cancers with these important driver mutations.

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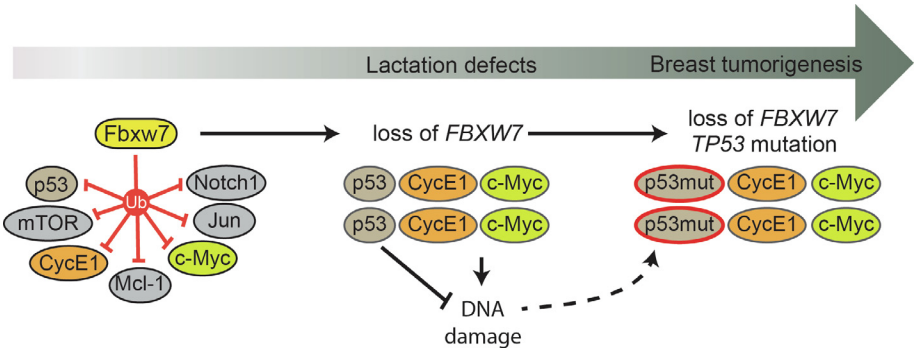

Fig. 1. Stepwise acquisition of *Trp53* mutation following *Fbxw7* loss in a model of breast cancer. Fbxw7 is a tumor suppressor that targets several key oncogenes, and also the tumor suppressor p53. Meyer et al. have identified that *Fbxw7* loss leads to lactation and involution defects in mice, and eventually to mammary tumors. This is associated with increased cyclin E1 and c-Myc activity, along with DNA damage. A second hit of *Trp53* mutation is probably induced by the increase in DNA damage, and will overcome any induction of p53 activity downstream of *Fbxw7* loss.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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