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AUTHOR'S VIEW

Sestrin1, a tumor suppressor that can be rescued

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ABSTRACT

SESTRIN1 is a tumor suppressor in follicular lymphoma that controls mTORC1 activity and it is inactivated by chromosomal deletions or epigenetically silenced by mutant $EZH2^{Y641X}$. Pharmacological inhibition of EZH2 promotes *SESTRIN1* re-expression and it restores its tumor suppressive activity, suggesting the possibility to epigenetically control mTORC1 activity.

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Follicular lymphoma (FL) is a common form of indolent B-cell malignancy characterized by numerous genomic alterations including chromosomal rearrangement, mutations, and epigenetic changes. In the context of tumor evolution, the acquisition of the chromosomal translocation t(14;18)(q32;q21), that promotes the over-expression of the anti-apoptotic protein BCL2, is an early event in FL development. Nevertheless, B-cells harboring this chromosomal re-arrangement require the accumulation of additional mutations and chromosomal copy number changes to exhibit tumorigenic capacity.[1,2] Deletions on chromosome 6q are one of the most frequent copy number alterations observed in FL patients. Tumorigenic B-cells harboring these alterations are positively selected in FL development and progression, indicating that the loss of multiple genes on chromosome 6q actively contributes to malignant B-cells transformation.[3] In addition to chromosomal aberrations, several epigenetic modifiers are frequently mutated in FL, including the histone methyltransferases *EZH2* and *MLL2* (gene name *KMT2D*), the histone acetyltransferase *CREBBP*, and the chromatin remodeling factor *ARID1A*.[4,5] Epigenetic modifiers can directly and indirectly activate or repress the expression of several genes, altering the FL transcriptomic profile.[6] Since both epigenetic changes and large chromosomal lesions simultaneously affect several genes, it is challenging from the sole analysis of genomic data to identify functionally relevant targets.

In our recent study, we used a functional genetic screen to identify new candidate tumor suppressors in FL targeted by large deletions on chromosome 6q. Through the screen analysis and the subsequent validation of the screen results in a chimeric animal model of FL, we were able to identify *SESTRIN1* as a new tumor suppressor in FL.[7] *SESTRIN1* is deleted in 20% of FL lymphoma patients, most of the deletions include several genes, and in rare cases, patients harbor focal deletions, which further pinpoints to *SESTRIN1* as an important target. In addition to chromosomal deletions, we found that *SESTRIN1* is epigenetically silenced by the mutated protein $EZH2^{Y641X}$ through increase of Histone3-Lysine-27-Methyl-3 (H3K27me3) and consequent hyper methylation of the *SESTRIN1* promoter.[7]

SESTRIN1 is a member of a protein family including *SESTRIN2* and *SESTRIN3*. These proteins are transcriptional targets of p53 (TP53, best known as p53)[8] and they function as guanine nucleotide dissociation inhibitors regulating the activity of the Rag-A (gene name *RRAGA*), Rag-B (gene name *RRAGB*), and mTORC1 complex.[9] In FL patients, the expression of *SESTRIN2* and *SESTRIN3* is not epigenetically regulated and these genes are rarely targeted by chromosomal deletions, indicating an exquisite dependency of B-cells on *SESTRIN1* activity. Indeed loss of *Sestrin1* is sufficient to drive lymphomagenesis in chimeric mouse model of FL.[7]

In response to genotoxic and cellular stress, p53 induces *SESTRIN1* expression. Cells exposed to nutrient deprivation or DNA damage activate protective programs to block or eliminate cells that have lost their integrity. p53 is the principal controller of genome integrity and cancer cells must inactivate p53 or bypass its activity to continue to proliferate. In lymphoma genomic alterations that directly target p53 are less frequent than in other tumors, indicating that malignant B-cells in FL have acquired alternative strategies to evade p53 action. We observed that the ability of p53 to activate *SESTRIN1* was significantly hampered in cells expressing mutated $EZH2^{Y641X}$. This implies that the increase of H3K27me3 on the *SESTRIN1* promoter not only represses the gene expression, but it also limits the ability of p53 to bind and induce expression of *SESTRIN1*. As a consequence, mTORC1 activity cannot be regulated and it remains active in cells exposed to genotoxic stress.

Recent studies have highlighted the central role of mTORC1 activity to sustain FL pathogenesis. Sequencing analysis

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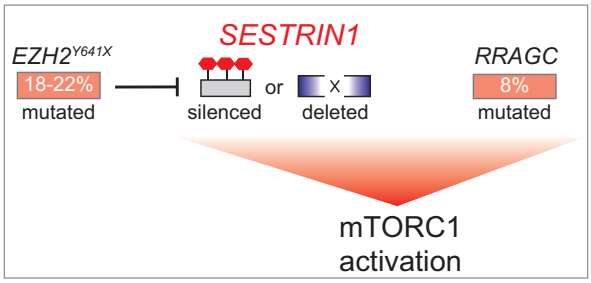

Figure 1. Several genomic lesions lead to the activation of mTORC1 signaling in Follicular Lymphoma (FL). *EZH2*^{Y641X} gain-of-function mutations occur in 18–22% of FL patients and it promotes *SESTRIN1* epigenetic silencing. *SESTRIN1* is also deleted in 20% of FL. These lesions are mutually exclusive with *RRAGC* mutations that usually occur in 8% of cases. Alterations in these genes contribute to sustain mTORC1 oncogenic activity in FL.

revealed mutations targeting *RRAGC* (best known as *Rag-C*) uniquely found in FL patients. Mutations in *RRAGC* tend to co-occur with mutations in *ATP6V1B2* and *ATP6AP1* genes,[10] but they are mutually exclusive with *SESTRIN1* deletions or epigenetic silencing.[7] Importantly, all of these genes are important regulators of mTORC1 activity (Fig. 1). Cells harboring mutations in *RRAGC* are less sensitive to nutrient deprivation, and amino acid withdrawal does not reduce mTORC1 activity. Similarly, loss of *SESTRIN1* contributes to sustain mTORC1 in response to DNA damage. Interestingly, the near mutual exclusivity of *RRAGC* and *SESTRIN1* alterations suggests that one of these two alterations is sufficient to unleash mTORC1 activity and promote follicular lymphomagenesis.

If Sestrin1 is silenced, it can be reawakened. If it is deleted, it cannot come back

Restoring the expression or the activity of a tumor suppressor gene is a major challenge in cancer therapy. A few years ago, we proposed to use a fusion antibody as potential therapeutic strategy to recover the activity of a soluble tumor suppressor, *EPHA7*[3]. Although this task is feasible as proof of principle, it has been arduous to translate this idea into a clinically valuable tool. Moreover, it remains unfeasible to directly re-express mutated or deleted tumor suppressors. In FL, chromosomal deletions targeting *SESTRIN1* are mutually exclusive with *EZH2* mutations, indicating that *SESTRIN1* is epigenetically silenced but its genomic locus is intact in patients expressing the EZH2^{Y641X} mutated protein. Currently, several EZH2 inhibitors are being tested in clinical trials. In our study, we show that the therapeutic efficacy of these drugs is, at least in part, linked to their ability to reactivate *SESTRIN1* expression. EZH2 inhibitors repress the methyltransferase enzymatic activity and are able to release the epigenetic block holding *SESTRIN1* expression. Reactivation of *SESTRIN1* translates in mTORC1 inhibition and decrease of protein translation, ultimately undermining tumor growth.

In summary, cells expressing mutated EZH2^{Y641X} are selected during the evolution of FL tumor for their ability to inhibit the expression of tumor suppressors. Indeed, while mutated *EZH2* can block the expression of multiple genes, its oncogenic role is unequivocally tied with the functional relevance of its targets. Consequently, the therapeutic efficacy of EZH2 inhibitor is strictly linked to their ability to restore the activity of tumor suppressors.

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The authors declare no competing financial interests.

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