Senescence after growth arrest: A mechanism by which CDK4/6 inhibitors can mediate their activity suppressing tumor progression


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Background: CDK4/6 inhibitors are being used to treat a variety of human malignancies. In well-differentiated (WDLS) and dedifferentiated (DDLS) liposarcoma we had previously suggested that their clinical promise might be associated with their ability to down-regulate the MDM2 protein. In cultured cell lines, the down-regulation of MDM2, after cells left the cell cycle following CDK4 inhibition, induces them to progress from quiescence into senescence. Today, we will present further evidence supporting the idea that senescence after growth arrest is a mechanism that can account for the activity of CDK4 inhibitors, at least in WD/DDLS.

Results: We have found that PDLIM7 physically associates with MDM2 and prevents MDM2 turnover in quiescent cells induced by treatment with palbociclib (PD0332991). However, if PDLIM7 is sequestered by an intracellular cadherin, CDH18, MDM2 turnover occurs following treatment with PD0332991, driving the quiescent cell into the senescent state. CRISPR knockout of CDH18 can prevent both MDM2 degradation and senescence in cells challenged with CDK4 inhibitor.

Establishing the clinical relevancy of this pathway, CDH18 expression is associated with clinical outcome and histologic subtype in patients with advanced WDLS and DDLS from our previous phase II trials. 92% of WDLS and 57% of DDLS had high CDH18 expression judged by immunohistochemistry. High expression of CDH18 in DDLS was associated with improved clinical outcomes.

Conclusions: This supports the hypothesis that the transition from quiescence to senescence has clinical relevance as a mechanism for this class of drugs.

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