Everolimus inhibits angiogenesis and lymphangiogenesis in TP53 mutant HNSCC via STAT3/HIF-1α/VEGF pathway

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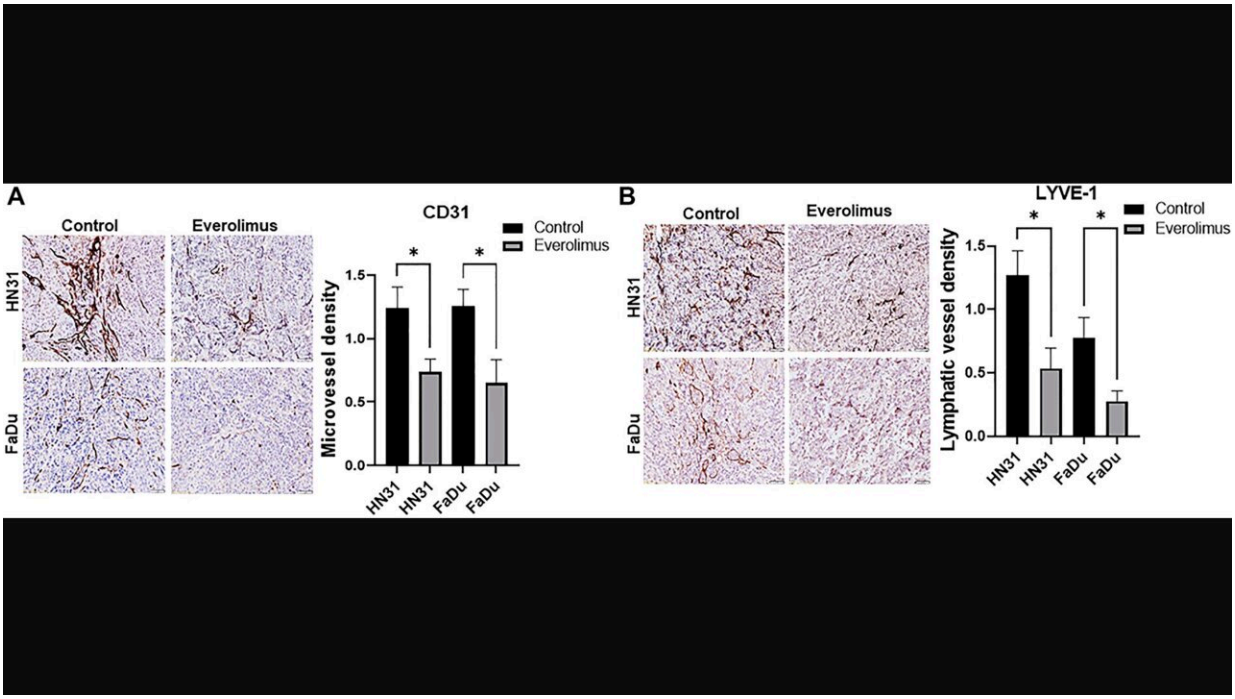

Everolimus reduces microvessel density (MVD) and lymphatic vessel density (LVD) in TP53 mutant HNSCC xenografts. Credit: *Oncotarget* (2023). DOI: 10.18632/oncotarget.28355

A new research paper was published in *Oncotarget*, titled, "Everolimus downregulates STAT3/HIF-1α/VEGF pathway to inhibit angiogenesis

and lymphangiogenesis in TP53 mutant head and neck squamous cell carcinoma (HNSCC)."

TP53 mutant head and neck squamous cell carcinoma (HNSCC) patients exhibit poor clinical outcomes with 50–60% recurrence rates in advanced stage patients. In a recent phase II clinical trial, adjuvant therapy with everolimus (mTOR inhibitor) significantly increased 2-year progression-free survival in p53 mutated patients. TP53-driven mTOR activation in solid malignancies causes upregulation of HIF-1α and its target, downstream effector VEGF, by activating STAT3 cell signaling pathway.

In this recent study, researchers Md Maksudul Alam, Janmaris Marin Fermin, Mark Knackstedt, Mackenzie J. Noonan, Taylor Powell, Landon Goodreau, Emily K. Daniel, Xiaohua Rong, Tara Moore-Medlin, Alok R. Khandelwal, and Cherie-Ann O. Nathan from LSU-Health Sciences Center investigated the effects of everolimus on the STAT3/HIF-1α/VEGF pathway in TP53 mutant cell lines and xenograft models.

"The role of mTOR inhibitors (mTORi) as potent growth inhibitory and antiangiogenic/anti-lymphangiogenic agents in HNSCC is well established," the paper explains. "Moreover, mTORi significantly suppressed baseline invasiveness of endothelial and HNSCC tumor cells. However, the underlying molecular mechanisms for mutant p53 protein-mediated activation of the mTOR pathway which drive the oncologic processes in HNSCC are yet to be elucidated."

Treatment with everolimus significantly inhibited cell growth in vitro and effectively reduced the growth of TP53 mutant xenografts in a minimal residual disease (MRD) model in nude mice. Everolimus treatment was associated with significant downregulation of STAT3/HIF-1α/VEGF pathway in both models.

Further, treatment with everolimus was associated with attenuation in tumor angiogenesis and lymphangiogenesis as indicated by decreased microvessel density of vascular and lymphatic vessels in HN31 and FaDu xenografts. Everolimus downregulated the STAT3/HIF-1α/VEGF pathway to inhibit growth and in vitro tube formation of HMEC-1 (endothelial) and HMEC-1A (lymphatic endothelial) cell lines.

"Our studies demonstrated that everolimus inhibits the growth of TP53 mutant tumors by inhibiting angiogenesis and lymphangiogenesis through the downregulation of STAT3/HIF-1α/VEGF signaling," write the researchers.

More information: Md Maksudul Alam et al, Everolimus downregulates STAT3/HIF-1α/VEGF pathway to inhibit angiogenesis and lymphangiogenesis in TP53 mutant head and neck squamous cell carcinoma (HNSCC), *Oncotarget* (2023). DOI: 10.18632/oncotarget.28355

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