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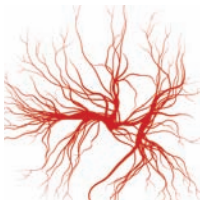
Techniques

Major Finding: Transduction of *ETV2* restored blood vessel–forming capabilities to mature human endothelial cells.

Concept: This altered the epigenome and transcriptome, reverting the cells to an adaptable fetal state.

Impact: This method could be used to study vasculature–parenchyma interactions in organoids and tumoroids.

NEW METHOD ENABLES DEVELOPMENT OF CUSTOMIZED VASCULATURE IN ORGANOIDS



Organoids and tumoroids have an invaluable place in cancer research; however, using them to study interactions between parenchymal cells and the vasculature that would grow around and within organs and tumors *in vivo* has been challenging because cultured adult endothelial cells are not efficient in forming new tissue-specific vessels. To address this, Palikuqi and colleagues developed "reset" vascular endothelial cells (R-VEC), which were produced via lentiviral transient transduction of *ETV2*, encoding a pioneer transcription factor that promotes vascular adaptation and lumen formation during early development. In serum-free medium, these R-VECs grew into three-dimensional vessels with continuous open lumens and apicobasal polarity, and R-VECs implanted into mice formed durable, non-leaky, branching vessels capable of transporting blood. RNA-sequencing experiments revealed that early-stage R-VECs exhibited upregulation of genes in pathways that regulate vasculogenesis, angiogenesis, GTPase activity, extracellular matrix remodeling, response to mechanical stimuli, and activation of the small GTPase RAP1, which is required for lumen formation. Chromatin immunoprecipitation–sequencing experiments showed that *ETV2* transduction promoted epigenetic changes that resulted in activation and priming of tubulogenic and vasculogenic genes and demonstrated that this was due to direct binding between ETV2 and promoters of upregulated genes, where ETV2 binding led to an altered histone-modification profile. Importantly, R-VECs were able to vascularize and conform to normal colon organoids and maladapt to colorectal cancer organoids. In colon organoids, R-VECs adjusted to normal organoids and expressed organotypic marker genes, including *PLVAP* and *TFF3*, whereas R-VECs in colorectal cancer organoids exhibited the aberrant gene expression characteristic of tumor endothelial cells, expressing genes such as *ID1*, *JUNB*, and *ADAMTS4*. In summary, this work lays the foundation for a new approach for investigating the cross-talk between vasculature and parenchymal cells that, in the cancer field, may be of particular use in uncovering how tumor vasculature acquires corrupted features and identifying druggable targets to block tumor growth and metastasis. ■

Palikuqi B, Nguyen DHT, Li G, Schreiner R, Pellegata AF, Liu Y, et al. Adaptable haemodynamic endothelial cells for organogenesis and tumorigenesis. Nature 2020;585:426–32.

Immunology

Major Finding: Tumor cells outcompeted T cells for methionine, causing epigenetic aberrations at *Stat5* in T cells.

Concept: *S*-adenosylmethionine is a cofactor for histone methyltransferases involved in epigenetic regulation.

Impact: This work links methionine metabolism to abnormal tumor-infiltrating T-cell epigenetics and function.

TUMOR CELLS DEPLETE METHIONINE VIA SLC43A2, CAUSING T-CELL DYSFUNCTION

Tumor-infiltrating cytotoxic T cells often exhibit dysfunctional phenotypes that have been linked to aberrant epigenetic patterns. Bian, Li, and colleagues found that $CD8^+$ T cells grown in methionine-free medium were apoptosis-prone and had low production of IFNγ and TNFα. Increased apoptosis was observed in T cells grown in supernatant from cultured tumor cells; this supernatant was found to be depleted of methionine. Additionally, transwell assays revealed that tumor cells could outcompete $CD8^+$ T cells for methionine in shared medium. T cells grown in tumor supernatant had abnormally low levels of methionine and *S*-adenosylmethionine, the methyl donor used as a cofactor by histone lysine methyltransferases; also, these T cells had reduced levels of histone 3 lysine residue 79 dimethylation (H3K79me2, an active mark found at promoters and 5′ regions of genes). Inhibition of the sole H3K79 methyltransferase DOT1L *in vitro* and T cell–specific deletion of *Dot1l in vivo* caused loss of T-cell H3K79me2, increased T-cell apoptosis, and defective T-cell IFNγ and TNFα production. Tumors in *Dot1l*-knockout mice grew at increased rates and had high levels of T-cell apoptosis and low levels of IFNγ, TNFα, and granzyme B. *Dot1l*-knockout T cells exhibited an apoptosis-linked gene signature with defective *Stat5* expression, leading to low levels of STAT5 and phosphorylated STAT5, an effect also seen when T cells were cultured with tumor-cell supernatant. T cells had high levels of H3K79me2 at the *Stat5* promoter when grown in normal medium, but this mark was depleted in T cells grown in tumor-cell supernatant. Mechanistically, methionine import via SLC43A2 by tumor cells, which expressed this transporter at high levels, enabled tumor cells to outcompete T cells for methionine. In transwell assays and *in vivo*, *Slc43a2* knockdown in tumor cells reduced T-cell apoptosis, raised T-cell H3K79me2, and increased T-cell IFNγ and TNFα production. Methionine supplementation in patients with colorectal cancer resulted in improved T-cell function. Collectively, these results establish a previously unknown link between methionine metabolism and epigenetically mediated T-cell dysfunction in tumors. ■

Bian Y, Li W, Kremer DM, Sajjakulnukit P, Li S, Crespo J, et al. Cancer SLC43A2 alters T cell methionine metabolism and histone methylation. Nature 2020;585:277–82.

AACR American Association for Cancer Research

CANCER DISCOVERY

New Method Enables Development of Customized Vasculature in Organoids

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