The impact of chemotherapeutic agents on the global chromatin profiles of human vascular endothelial and smooth muscle cells

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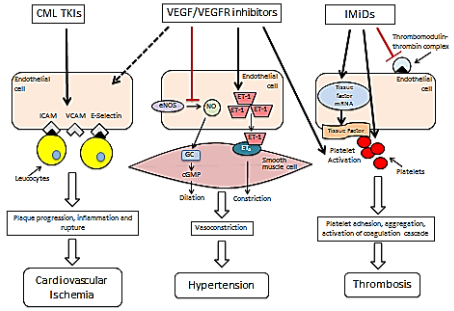
Background

Molecularly targeted anti-cancer therapeutics have revolutionized cancer treatment. Cardiovascular toxicity can be a dose limiting side effect of these agents. Vascular toxicities include hypertension, increased cardiovascular ischemic events and increased risk of arterial and venous thrombosis. The mechanisms of vascular toxicities are unclear and may be related to on- or off-target effects in vascular cells. The blood vessel is made up of an inner lining of endothelial cells surrounded by smooth muscle cells. The endothelial cell is thought to be the central mediator of vascular toxicity.



Hypothesis

Anti cancer agents cause changes in the chromatin profile of vascular cells that differ from their effects on cancer cells. Understanding these differences could lead to safer cancer therapies.

Methods

We used the global chromatin profiling assay (GCP) to study the effects of chemotherapeutics on primary human umbilical vein endothelial cells (HUVEC) and human aortic smooth muscle cells (HuAoSMC) and compared these to profiles from cancer cell lines (MCF7-breast, PC3-prostate, A549-lung, A375-skin, NPC-neuronal progenitor cells).

Epigenetic modulators	
Drug	Mechanism
Vorinostat	HDAC inhibitor
Decitabine	DNMT inhibitor
JQ1-S	Bromodomain inhibitor
GSK126	EZH-2 inhibitor
UNC-0646	G9a inhibitor
GSK-J4	Histone demethylase inhibitor
Resveratrol	SirT1 activator
Geldanamycin	HSP 90- inhibitor

Kinase inhibitors	
Drug	Mechanism
Pazopanib	VEGFR, PDGFR inhibitor
Nilotinib	BCR-Abl inhibitor
LY-294002	PI3-K inhibitor
Okadaic Acid	PP1 and PP2a inhibitor
Tofacitinib	Jak3 inhibitor
SP600125	Jnk inhibitor
Losmapimod	p38 MAPK
AR-A014418	GSK3 inhibitor
Staurosporine:	Pan kinase inhibitor

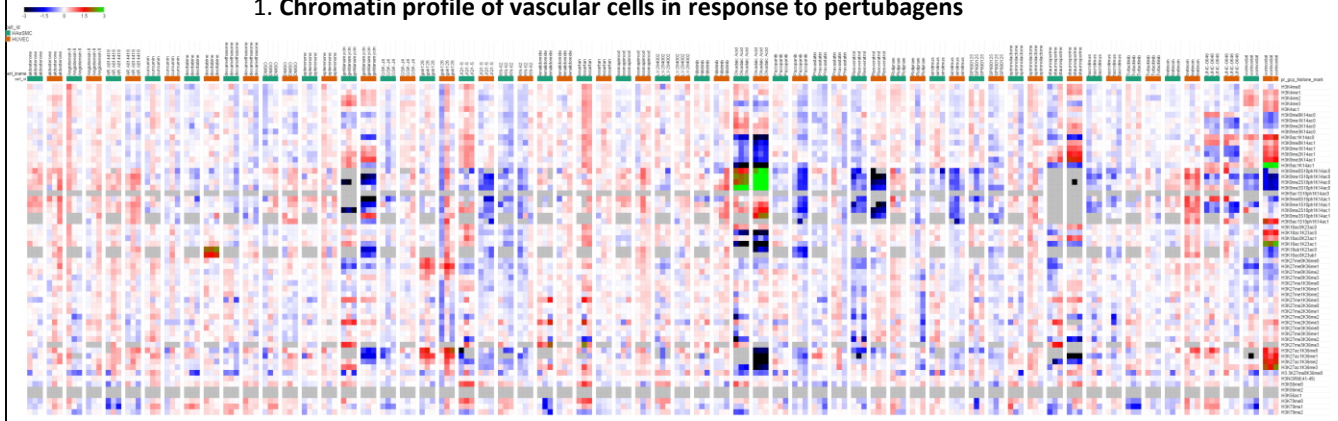
Others	
Drug	Mechanism
Tretinoin	RAR agonist
Tacrolimus	Calcineurin inhibitor
Sirolimus	mTOR inhibitor
Lenalidomide	Immunomodulator
Curcumin	NFkB inhibitor
KN-62	CaMKIIalpha inhibitor
Pravastatin	HMGCoA reductase inhibitor
Rolipram	PDE4 inhibitor

MR agonists/antagonists
Aldosterone
Angiotensin II
Eplerenone
Losartan
Spironolactone
Dexamethasone

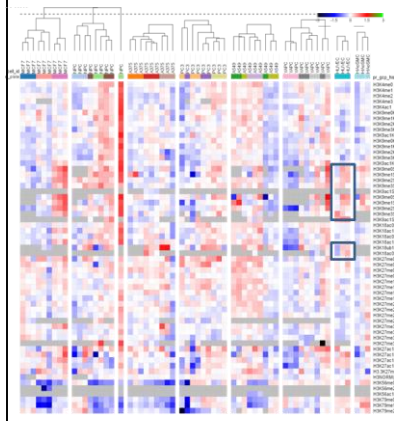
Red: used in clinical oncology, no vascular effect.
Green: used in clinical oncology, known vascular adverse effects.

Results

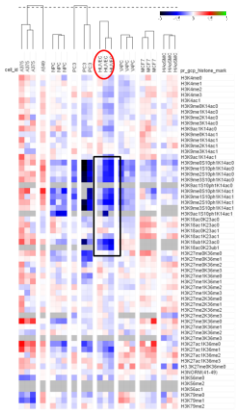
1. **Chromatin profile of vascular cells in response to pertubagens**



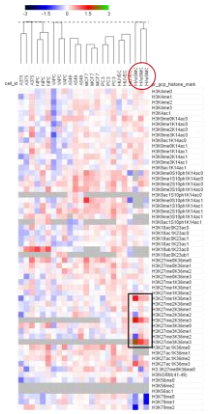
2. Basal Chromatin Profile of Cancer Compared to Vascular Cells (with DMSO control)*



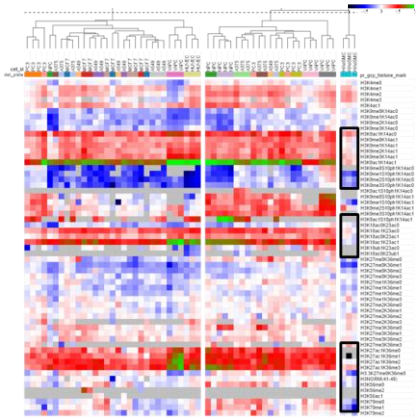
3. Pazopanib decreases H3S10 phosphorylation and K18/K23 ubiquitination in HUVEC*



4. Lenalidomide increases H3K36 trimethylation in HuAoSMC*



5. The consistent chromatin profile of Vorinostat across all cell types previously tested is distinct in HuAoSMC†



*Data normalized to row median of processing plate, clustered by Euclidian distance and grouped by cell type.
†Data normalized to row median of processing plate, clustered by Euclidian distance.

Conclusions

The chromatin profile of HUVEC and HuAoSMC are most similar to each other and differ from cancer cell lines.

Small molecule anti-cancer agents produce unique chromatin marks in vascular cells.

Future Directions:

Further analysis of these GCP data will be combined with P100 phosphoproteomic data from these human vascular cell lines. The results will enhance our understanding of critical pathways in vascular cells and identify potential mechanisms of vascular toxicity.

The resulting hypothesis will be further explored in other models to identify cancer therapies with safer cardiovascular profiles.