Tailoring treatment for Erdheim-Chester disease: focus on ECD microenvironment

Marina Ferrarini, MD

Laboratory of Lymphoid Malignancies
Division of Experimental Oncology

ECD Global Alliance Medical Symposium
Paris, Hôpital Pitié-Salpêtrière
September 15, 2016
A unifying disease model for ECD

Cavalli et al, 2014
Vemurafenib treatment in Erdheim-Chester disease

Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation

Reproducible and Sustained Efficacy of Targeted Therapy With Vemurafenib in Patients With BRAF V600E-Mutated Erdheim-Chester Disease

Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V6000 Mutations
Not all ECD patients bear the BRAFV600E mutation or known targetable mutations.

Vemurafenib treatment mostly results in partial clinical responses in ECD patients.

Vemurafenib treatment may be associated with severe side effects and resistance or relapse.

The molecular mechanisms exerted by vemurafenib on ECD tissues are unknown.
Aims

- to investigate the pathogenic effects of ECD microenvironment to identify new target molecules and pathways

- to exploit the bioreactor technology for culturing ECD tissues to assess the impact of drugs on both ECD histiocytes and their surrounding microenvironment
### ECD exudates as a surrogate microenvironment

<table>
<thead>
<tr>
<th></th>
<th>TNF-α</th>
<th>IL-1β</th>
<th>IL-6</th>
<th>CXCL8</th>
<th>CCL2</th>
<th>CCL4</th>
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<tbody>
<tr>
<td><strong>PF1</strong></td>
<td>3</td>
<td>0</td>
<td>4392</td>
<td>23</td>
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<td><strong>PF2</strong></td>
<td>69</td>
<td>8.4</td>
<td>8335</td>
<td>2129</td>
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<td>78</td>
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<td><strong>PF3</strong></td>
<td>30</td>
<td>0</td>
<td>30680</td>
<td>70</td>
<td>99</td>
<td>81</td>
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<tr>
<td><strong>PF4</strong></td>
<td>13.7</td>
<td>57.2</td>
<td>4056</td>
<td>47</td>
<td>4742</td>
<td>72</td>
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<thead>
<tr>
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<th>sTNF-Rs (ng/ml)</th>
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<tr>
<td>PB</td>
<td>sTNF-RI sTNF-RII</td>
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<tr>
<td><strong>(n=4)</strong></td>
<td>1.48 ±1.25 0.33 ±0.24 16.4 ±6.8 36.4 ±14.3 68.4 ±15 97.6 ±15.2</td>
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<tr>
<td><strong>(n=8)</strong></td>
<td>0.43 ±0.26 0.61 ±0.17 2.54 ±1.4 9.9 ±2.84 55.6 ±11.6 91.6 ±19.6</td>
</tr>
</tbody>
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**Ferrero et al. 2013 Rheumatology**
TNF-α in ECD pericardial fluid affects endothelial functions

Ten Hagen et al. 2008

Ferrero et al. 2013 Rheumatology
ECD pericardial fluid promotes monocyte chemotaxis
ECD pericardial fluid affects macrophage phenotype

Phenotypic activation and pharmacological outcomes of spontaneously differentiated human monocyte-derived macrophages
Serena Tedesco, Chiara Bolego, Alice Toniolo, Alberto Nasi, Gian Paolo Fadini, Massimo Locati, Andrea Cignarella

NT

PF

\[ \Delta \text{MFI} = 65 \]

\[ \Delta \text{MFI} = 51 \]

Red Oil

CD206

Resting LPS/IFN\(\gamma\)
RCCSTM bioreactor preserves architecture of normal and cancer tissues

2 weeks

LDH (U/L)

VEGF (ng/ml)
Culture in RCCSTM Bioreactor allows drug testing in Multiple Myeloma tissues

Ferrarini et al, 2013 PlosOne
ECD tissues secrete cytokines and chemokines in culture in bioreactor

day 4
Cytokine- and BRAF-inhibitors modulate cytokine/chemokine release in supernatants from ECD tissues

day 4

Patient 1

- TNF-α
- IL-8
- IL-6*
- IL-1β

Patient 2

- TNF-α
- IL-8
- IL-6*
- IL-1β

CCL4
- CCL2

IL-6* concentration in ng/ml

Dagna et al, 2012 JCO
vemurafenib treatment modulates cyto-chemokine production by BRAF-mutated ECD tissues.
vemurafenib affects viability, proliferation and cytokine release in human BRAF-mutated melanomas
vemurafenib treatment does not affect proliferation or survival of ECD histiocytes in short-term culture.
Senescence-inducing stimuli and main effector pathways

van Deursen, 2014 Nature
Response of BRAF-Mutant Melanoma to BRAF Inhibition Is Mediated by a Network of Transcriptional Regulators of Glycolysis


APRIL 2014  CANCER DISCOVERY | 423

See related commentary on pg 2923

BRAF Inhibition Generates a Host–Tumor Niche that Mediates Therapeutic Escape

Inna V. Fedorenko, Jennifer A. Wargo, Keith T. Flaherty, Jane L. Messina, and Keiran S.M. Smalley

Journal of Investigative Dermatology (2015) 135, 3115–3124; doi:10.1038/jid.2015.329; published online 10 September 2015
Conclusions/Perspectives

- The cytokine milieu in ECD lesions is endowed with pathogenic activities, whose understanding may disclose new therapeutic targets.
- The RCCS™ bioreactor allows culture of ECD tissues and the assessment of the impact of drugs, including cytokine- and BRAF-inhibitors.
- The technology can be further exploited as a novel tool to identify mechanisms of action/resistance of BRAF/MEK inhibitors on ECD histiocytes and their microenvironment for future combination therapies.
# Acknowledgements

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<td><strong>Istituto Nazionale Tumori</strong></td>
<td><strong>Consorzio MIA, University of Milano-Bicocca</strong></td>
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<td><strong>University “La Sapienza”, Rome</strong></td>
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Kathy Brewer
ECD Global Alliance,
DeRidder, LA