The Role of Chemical Co-Solvents on G-Quadruplex structures in the c-MYC and VEGF proto-oncogene promoters

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Overview

Introduction to Cancer
New Targeting Strategy
Proto-oncogenes c-MYC and VEGF
Results
Future Work
Cancer in the United States

- 2nd leading cause of death
- 1 in 4 people will develop cancer in their lifetime
Targeting Cancers Achilles Heel

- G-quadruplex
- i-Motif
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Targeting Cancers Achilles Heel

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DNA Secondary Structures and Base Pairing Interactions

Watson & Crick Base Pairing

G-quadruplex

i-Motif
Hallmarks of Cancer
c-MYC in Cancer

- Over expressed in more than 70% of all cancers
- Extremely difficult to drug

Diagram:
- c-MYC
  - Self-sufficiency in growth signals
  - Evading apoptosis
  - Deregulated Metabolism
  - Insensitivity to anti-growth signals
VEGF in Cancer

- Vascular Endothelial Growth Factor
- Regular function is formation of new blood vessels
  - Provides oxygen and nutrients to cells
- Tumor cells can “turn on”
  - Angiogenesis
- DNA footprinting data shows formation of G-quadruplex could have potential transcriptional regulation
Intracellular stresses mimicked by Molecular Crowding Agents

<table>
<thead>
<tr>
<th>Crowding Agents</th>
<th>Dehydrating Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ficoll70</td>
<td>Glucose</td>
</tr>
<tr>
<td>Dextran Sulfate</td>
<td>Glycerol</td>
</tr>
<tr>
<td>PEG-300</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>Sucrose</td>
<td></td>
</tr>
</tbody>
</table>
Results
c-MYC: Crowding Agents

50mM Tris-HCl 10mM KCl
c-MYC: Dehydrating Agents

**MYC Glycerol**

- Control
- 10%
- 20%
- 30%
- 40%

**MYC Glucose**

- Control
- 10%
- 20%
- 30%
- 40%

**MYC Acetonitrile**

- Control
- 10%
- 20%
- 30%
- 40%

50mM Tris-HCl 10mM KCl


**VEGF: Crowding Agents**

**VEGF PEG 300**
- Control
- 10%
- 20%
- 30%
- 40%

**VEGF Dextran**
- Control
- 10%
- 20%
- 30%
- 40%

**VEGF Sucrose**
- Control
- 10%
- 20%
- 30%
- 40%

**VEGF Ficoll70**
- Control
- 10%
- 20%
- 30%
- 40%

50mM Tris-HCl 10mM KCl
VEGF: Dehydrating Agents

VEGF Glycerol

VEGF Acetonitrile

VEGF Glucose

50mM Tris-HCl 10mM KCl
Saturation Points

MYC Sucrose Saturation Determination

- Wavelength (nm)
- Molar Ellipticity
- Control
- 10%
- 20%
- 30%
- 40%

- at 262nm
- at 240nm
Future Work: Drug Discovery

- Thermal Melt at saturation points with each co-solvent
- Begin screening c-MYC and VEGF G-quadruplexes with varies compounds in nuclear conditions
  - FRET melts
  - Cytotoxicity Assays
Acknowledgments

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Questions?

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References


