Presenter Disclosure Information

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The following relationships exist related to this presentation:

No Relationships to Disclose
Identification of colon cancer associated antigens: key therapeutic targets in the prevention of disease relapse or progression


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Introduction

• Colorectal cancer (CRC) is the second leading cancer in the US
  – 146,000 new cases and 50,000 deaths
• Adaptive immune response may play role in preventing tumor recurrence
• Vaccine could boost cellular immunity
• Few defined immunogenic proteins
• Can we identify antigens suitable for a CRC vaccine?
Methods

• Systematic literature search using key words, i.e. colon cancer, prognosis, multivariate analysis
  – 125 papers identified

• 8 proteins evaluated based on:
  – Incidence of expression
  – Independent predictor of poor prognosis
  – Independent predictor of early disease recurrence
  – Known biologic function

• Algorithm to identify peptides predicted to be high affinity binders across multiple HLA DR alleles

Park, K et al. Ca Res, 2008
<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
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<tbody>
<tr>
<td>CDC25B</td>
<td>cell cycle overexpression</td>
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<tr>
<td>COX-2</td>
<td>cell proliferation, inflammation</td>
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<tr>
<td>EBAG9/RCAS1</td>
<td>inhibits cell growth/ apoptosis of T,B, NK cells</td>
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<tr>
<td>EGFR*</td>
<td>cell division, migration, angiogenesis</td>
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<tr>
<td>FASCIN</td>
<td>cell-cell interaction and adhesion, actin-based structures, cell locomotion</td>
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<tr>
<td>IGF1R*</td>
<td>enhances cell survival, anti-apoptotic agent</td>
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<tr>
<td>PRL-3/PTP4A3</td>
<td>cancer cell migration and proliferation, angiogenesis, invasion and metastasis</td>
</tr>
<tr>
<td>VCP</td>
<td>anti-apoptotic function and metastasis via activation of NF-kappa B signaling pathway</td>
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</tbody>
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CDC25B phosphatase heat map

Predicted binding x # DR alleles
Top quartile: Orange-red-brown
Mid quartiles: Yellow-gold
Bottom quartile: Blue-green
Predicted “hot spot” density varies

<table>
<thead>
<tr>
<th>PRL-3</th>
<th>p12-30, p33-53, p104-122, p124-142</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCP</td>
<td>p49-65, p82-102, p138-156, p161-180</td>
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</table>
IFN-γ ELISPOT response to candidate antigens

( n=10) candidate antigens

PPM from CSPW
Gene expression of candidate antigens in CRC cell lines

MSI (HCT 116), CIMP (RKO, SW48), CIN (FET, SW480)
Conclusions

• Biologically relevant CRC associated proteins can be identified:
  – Associated with prognosis
  – Potentially overexpressed in majority of CRC

• Epitopes predicted to bind multiple DR, derived from candidate antigens, elicit T cell responses in CRC patients > controls

• Candidate antigen gene expression across different CRC phenotypes

• These antigens may represent novel immunologic targets for CRC
Acknowledgements
Candidate antigen specific IgG antibody response

Positive: Mean + 2 SD of controls