Regulation of the BH3-only protein PUMA by growth factor signalling

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Abstract

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P53 Upregulated Modifier of Apoptosis (PUMA), a pro-apoptotic member of the Bcl-2 family, is transcriptionally activated by p53 and is a key effector of p53-dependent apoptosis. We show that PUMA protein is subject to rapid post-translational regulation by phosphorylation at a conserved residue, serine 10, following serum or Interleukin-3 (IL-3) stimulation. Serine 10 is not within the BH3 domain and PUMA phosphorylated at serine 10 retained the ability to co-immunoprecipitate with anti-apoptotic Bcl-2 family members. However, phosphorylated PUMA was targeted for proteasomal degradation indicating that it is less stable than unphosphorylated PUMA. Importantly, we identified NEMO/IKK1/IKK2 as the kinase complex that interacts with and phosphorylates PUMA thereby also demonstrating that IL-3 activates NFκB signalling. This thesis therefore identified and characterised a novel survival pathway with important implications for IL-3 signalling and haemopoietic cell development.
Declaration

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Jarrod J Sandow

January 2011
Publications arising from this Thesis


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<th>Abbreviation</th>
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<tbody>
<tr>
<td>4-OHT</td>
<td>4-hydroxytamoxifen</td>
</tr>
<tr>
<td>CHX</td>
<td>Cycloheximide</td>
</tr>
<tr>
<td>CID</td>
<td>Collision-induced dissociation</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>ETD</td>
<td>Electron-transfer dissociation</td>
</tr>
<tr>
<td>FBS</td>
<td>Foetal Bovine Serum</td>
</tr>
<tr>
<td>FDM</td>
<td>Factor dependent myeloid</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>HA</td>
<td>Haemagglutinin</td>
</tr>
<tr>
<td>IL-3</td>
<td>Interleukin-3</td>
</tr>
<tr>
<td>IL-5</td>
<td>Interleukin-5</td>
</tr>
<tr>
<td>IP</td>
<td>Immunoprecipitation</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>MOMP</td>
<td>Mitochondrial outer membrane permeabilisation</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour Necrosis Factor alpha</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>Wt</td>
<td>Wild type</td>
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