NF\textsubscript{κ}B and Natural Product

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Outline

I. B cells and NFκB
   • B Cells, immunoglobulin
   • NFκB and its mechanism of action
   • NFκB activation and inhibition
   • Natural products as NFκB inhibitors

II. Syntheses of some NFκB inhibitors
   • Lupeol
   • Cycloepoxydone
B Cells

- B cells are lymphocytes that play a large role in the humoral immune response.
- The principal functions of B cells are to make antibodies against antigen, perform the role of antigen-presenting cells (APCs) and eventually develop into memory B cells.
- Essential component of the adaptive immune system.

http://en.wikipedia.org/wiki/B_cells
http://www.biooncology.com/images/therapeutic-targets/b-cell-lg.jpg&imgrefurl
A typical antibody is composed of two immunoglobulin (Ig) heavy chains and two Ig light chains.

The immunoglobulin (antibody) light chain is the small polypeptide subunit of an antibody.

Two types of light chain in humans and other mammals:
- kappa (κ) chain, encoded by the immunoglobulin κ locus (IGK@) on chromosome 2.
- lambda (λ) chain, encoded by the immunoglobulin λ locus (IGL@) on Chromosome 22.
NFκB

- NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of DNA.

- NFκB was first discovered in the lab of Nobel Prize (1975) laureate David Baltimore in 1986.

- NFκB family members share structural homology with the retroviral oncoprotein v-Rel, resulting in their classification as NFκB/Rel proteins.

- There are 5 proteins in the mammalian NFκB family:

<table>
<thead>
<tr>
<th>Class</th>
<th>Protein</th>
<th>Aliases</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NF-κB1</td>
<td>p105 → p50</td>
<td>NFKB1</td>
</tr>
<tr>
<td></td>
<td>NF-κB2</td>
<td>p100 → p52</td>
<td>NFKB2</td>
</tr>
<tr>
<td>II</td>
<td>RelA</td>
<td>p65</td>
<td>RELA</td>
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<tr>
<td></td>
<td>RelB</td>
<td></td>
<td>RELB</td>
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<tr>
<td></td>
<td>c-Rel</td>
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</tbody>
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http://en.wikipedia.org/wiki/NF-κB.
Mechanism of NFκB Action

- NFκB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, uv, oxidized LDL, bacterial or viral antigens.

- NFκB is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival.

- NFκB belongs to the category of “rapid-acting” primary transcription factor.

http://en.wikipedia.org/wiki/Immunoglobulin_light_chain
Aberrant NFκB Activation

• Incorrect regulation of NFκB has been linked to cancer, inflammatory and autoimmune disease, septic shock, viral infection, and improper immune development.

• In many tumors and inflammatory disease, such as inflammatory bowel disease, arthritis, septis, gastritis, asthma, atherosclerosis, NFκB was found to be constitutively active.

Inhibition of NFκB

- Methods of inhibiting NFκB has potential therapeutic application in cancer and inflammatory diseases.
- NFκB serves an important immune function, its absence can result in severe immuno-deficiency.
- NFκB inhibitors are most likely to be used as adjuvants along with other cancer therapies.

Natural Inhibitors of NFκB

Lupeol

Cycloepoxydon

Andrographolide

6-Hydroxythionapharidine

Gliotoxin

Parthenolide

Paclitaxel

Bryostatin 1

Food and Cancer Chemoprevention

Resveratrol
(wines, grape juice, peanut, mulberry, blueberry, cocoa powder, dark choclate)

Isothiocyanates
(wasabi, horseradish, mustard, radish, brussels sprout, watercress, nasturtiums)

Procyanidins
(apple, cinnamon, cocoa beans, grape seed, grape skin, wines, bilberry, cranberry, black currant, green tea, black tea)

Epigallocatechin gallate
(green tea)

Curcumin
(turmeric, ginger)

Genistein
(fava beans, soy beans, kudzu, psoralea, coffee)

Syntheses of some NF$_{\kappa}$B inhibitors

- **Lupeol**
  - Stock’s synthesis
  - Corey’s synthesis

- **Cycloepoxydone**
  - Porco, Jr’s synthesis
  - Mehta’s synthesis
Stock’s Synthesis of Lupeol

Stock’s Synthesis of Lupeol

Corey’s Synthesis of Lupeol

Corey’s Synthesis of Lupeol

1. Li, NH₃/THF, −78 °C
2. KOt-Bu, THF
3. TBSCI, DMF

83% over 3 steps

1. LHMDS, THF
2. LiBH₄, THF

72%

MsCl, NEt₃, CH₂Cl₂
−20 °C to 0 °C

90%

Porco, Jr’s Synthesis of cycloepoxydon

Porco, Jr’s Synthesis of cycloepoxydon

Mehta’s Synthesis of cycloepoxydon

Mehta’s Synthesis of cycloepoxydon

Summary

• NFκB is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival. It is essential component of the adaptive immune system.

• Improper regulation of NFκB has been linked to cancer, inflammatory and autoimmune disease, septic shock, viral infection, and improper immune development.

• Methods of inhibiting NFκB has potential therapeutic application in cancer and inflammatory diseases.