CD8 T cell-mediated Antitumor Effect of Imiquimod in a Mouse Model of Breast Cancer

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TLR Activation - “the Danger Signal”

- Imiquimod: binds TLR7
- Activates innate and adaptive immune response
- Anti-viral and anti-tumor effect

*Akira et al, Nat. Immunol, 2001*
Chest Wall Recurrence in Breast Cancer

Kolodziejski L et al, Breast J, 2005

Can we use imiquimod?
Animal model of breast cancer

- neu-tg mice [FVB/N-TgN (MMTVneu)-202Mul ]
- 70% of mice develop HER2+ tumor at 7-10 months of age
- Imiquimod or vehicle treatment started at palpable tumor
Topical Imiquimod Inhibits Tumor Growth

![Graph showing the inhibitory effect of Imiquimod on tumor growth.](image)

- **Vehicle**
- **Imiquimod**

Tumor volume in mm³ over time in days.
**Imiquimod Inhibits Development of Metastasis**

<table>
<thead>
<tr>
<th></th>
<th>Imiquimod</th>
<th>Vehicle</th>
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</thead>
<tbody>
<tr>
<td>Multilobed tumor</td>
<td>2/11</td>
<td>8/10</td>
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<tr>
<td>Lung metastases</td>
<td>0/11</td>
<td>3/10</td>
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[Image: histological section showing parenchyma and airway]
The Tumor Inhibitory Effect of Imiquimod Persists After Treatment Withdrawal
Imiquimod Inhibits the Proliferation of Tumor Cells

PCNA staining

control

Imiquimod

Cyclin D1 mRNA level

p=0.02

control

Imiquimod
Down-regulation of Cell Cycle-related Genes after Imiquimod Treatment
Genes Up-regulated by Imiquimod

- **Chemokine and Cytokine Genes**
  - Ccl2, Ccl3, Ccl4, Ccl5, Ccl7, Ccl8, Ccl9, Ccl11, Ccl12, Ccr5, Cx3cl1, Cxcl1, Cxcl9, Cxcl12, Cxcl16, Ifngr1, Il1b, Il10, Il13ra1, Il18r1, Tnf

- **Antigen Presentation**
  - B2m, Tap2, Tapbp, H2-Bf, H2-L, H2-Q6, H2-Q7

- **Other Immune Function Related Genes**
  - Vav1, Tlr4, Tlr2, umh2, Oas42, Oas6, Oas11b, Ap2b1, Ly80, Ly8e, Ly9c, Ly6a, Ifi30, Ifi31, Cbp1, G1p2, T2d29, Td169, Td106, Cd86, Cd72, Cd69, Cd54, Cd53, Cd32, Cd40, Cd72, Cd16, Cd14

- **Complement System**
  - C1qa, C1qb, C1qg, C2, C3, C4
Imiquimod Induces Expression of Immune Effector Molecules

Granzyme B mRNA level

Perforin mRNA level

p=0.01

p=0.03
Summary

- Topical Imiquimod stops the growth of spontaneous mammary tumors in neu-tg mice

- Imiquimod inhibits lung metastasis and the tumor inhibitory effect persists after treatment withdrawal

- Imiquimod changes the tumor microenvironment by up-regulating the expression of MHC I on tumor cells and recruiting CD8 T cells.

- The tumor inhibitory effect of imiquimod is dependent on CD8 T cells.
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