- When used in combination with dexamethasone, F8-IL4 was able to cure mice with established CIA

Macrophage polarization
~~Pic~~

GMCSF preferentially induces CCL17 production while CCL22 secretion is favoured by IL4

CCR4 ligands: CCL17 & CCL22
- CCR4 is a 7 transmembrane GPCR
- CCR4 ligands bind to R via an overlapping unique region
- CCL17 is proposed to recruit Th17 while CCL22 attracts Tregs

Th17/Treg imbalance in RA patients
Image

Summary: What to know
- Understand 5 signs of inflammation
- Main features of acute vs chronic inflammation & cell types
- Characteristics of RA
- Relevance of preclinical arthritis models (& cell types involved)
- Novel treatment options of RA

L17 Cancer signaling

11/4 Tuesday Rodney Luwor

☆ important

Overview
- EGFR/Erb family
- Complexity of signaling
  - Different ligands, receptor combinations, signaling pathways, cell behavior/fate
- Cancer complexity
  - Alterations in R, mutations in downstream molecules, implications
- Translational significance
  - Anti-EGFR therapy & KRas mutation

EGFR – epidermal growth factor receptor
- Ligand binds to EGFR's binding domain
- Leads to (P) of R
- Activation & docking of adaptor proteins
- Drives signaling → gene transcription

ErbbB family
- 4 members

- Interactions amongst family leads to different types of signaling pathways

EGFR expression in tumours
- Large % of patients have over-expression of EGFR
- High expression = poor outcome
- Tumours with high EGFR expression
    - Prostrate, breast, colorectal, renal…

☆ Results of enhanced EGFR signaling

Proliferation
- Increase expression of proteins involved in cell cycle progression (CDK2)
- decreases expression of cell cycle checkpoint proteins

Survival & resistance to therapy
- Increased anti-apoptotic protein expression (Bad)
- decreases pro-apoptotic proteins

Angiogenesis
- Increases pro-angiogenic proteins (VEGF, IL8)

Invasion/metastasis
- Increases expression of proteins involved in extracellular matrix degradation (MMP9) & survival proteins

☆ Mechanisms of enhancing EGFR signaling used by cancer cells
- EGFR over-expression
- EGFR mutation
- Increased autocrine signaling
- Enhanced downstream signaling by mutation
- Reduced or loss of phosphatase expression

1. EGFR over-expression
- Over-expression of ligand or R → over signaling

2. EGFR mutation
- Don't need ligand, always switch on → more signaling → increased survival/anti-apoptosis, angiogenesis, proliferation, metastasis (pro-cancer effects)

3. Increased autocrine signaling through increased ligand expression
- More ligand → more signaling → increased pro-cancer effects

4. Enhanced downstream signaling by mutation
- In many cancer cells, RAS is constitutively active
- RAS, RAF, PI3K constitutively active → increased pro-cancer effects

5. Reduced or loss of phosphatase expression
- mutation of PTEN common in tumour cells

- PTEN inhibits conversion of PI3K → AKT
- PI3K to AKT signaling will now be continuously
- more signaling → increased pro-cancer effects

Pro-cancer effects
- increased proliferation
- chemotherapy resistance
- survival / anti-apoptosis
- angiogenesis
- metastasis

Cetuximab
- Chimeric monoclonal Ab to the EGFR
- Approved for metastatic colorectal carcinoma & head and neck squamous cell carcinoma
- However, major tumour regression is observed in only 10-30% of advanced unselected cancer patients that respond to this drug
- Not significant enough

KRas mutation & cetuximab
Studies found
- 30-40% mCRC patients have KRas mutations
- cetuximab only blocks upstream
- downstream effects still going on, hence not much improvement90-95% patients w Kras mutation x respond to cetuximab & not treated with it
- patients w KRas mutations x treated w cetuximab (pointless)