Recent interdisciplinary studies provide insight into the next generation of Rheumatoid Arthritis treatments

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What is Rheumatoid arthritis

- Rheumatoid arthritis (RA): a chronic inflammatory disease that mainly targets the synovial membrane, cartilage and bone
- Disease modifying anti-rheumatic drugs (DMARDs) are used to treat it
- Examples
  - Enbrel (etanercept)
  - Remicade (infliximab)
  - Humira (adalimumab)
  - Methotrexate

New Treatments?

- Recent studies across many disciplines have been conducted to bring about new treatments
- Some experiments involve collagin-induced arthritis (CIA) in mice
- Some disciplines include:
  - Rheumatology
  - Nuclear Medicine
  - Immunology
  - Molecular Pharmaceutics

Treatment Categories

- Fusion Proteins and Antibodies
- Micro-RNAs
  - Metalloproteinases and Osteoprotegerin
- Binding Immunoglobulin Protein

Fusion Proteins and Antibodies

- Fusion Proteins
  - Target cytokines (small cell signaling proteins) to reduce inflammation
  - Usually a protein + antibody
  - Better able to taget affected joints
  - Enbrel (Prescribed)
  - Dekavil (Still in clinical trials)
- Antibodies
  - Same effect as fusion protiens
  - More antibody-based drugs are available for prescription
  - Remicade (Prescribed)
  - Humira (Prescribed)
  - SIP(SP3) (Unknown)

Metalloproteinases (MMPs)

- A group of more than 20 zinc-containing extracellular proteinases that are capable of degrading multiple components of the extracellular matrix
- Up-regulated in many diseases (including arthritis)
- In the past, researchers unsuccessfully attempted to use radiolabeled MMP inhibitors in order to image tumors
- Later, radiolabeled monoclonal antibodies specific to individual MMPs were used
  - Antibody SIP(SP3) was the most successful

Osteoprotegerin

- A naturally occurring inhibitor of OPGL
- OPGL: aka. Receptor Activator of Nuclear Factor kB Ligand (RANKL)
  - Essential factor for osteoclast differentiation from monocyte/macrophages
  - Located in the synovial membrane of RA patients, along with its receptor RANK
  - A fine balance between RANKL/RANK/OPG is required otherwise risk of having RA is increased
- A targeted therapy using OPG would mitigate bone damage in human RA

Micro-RNAs

- Small non-coding RNAs
- Used to investigate the expression of MMPs and OPGs
- Experimenting with them:
  1. Undergo luciferase reporter assays to examine the predicted effects of on-target mRNAs
  2. Tissues are transfected to over-express an mi-RNA and then analyzed
  3. Inhibition studies are also performed

Micro-RNA examples

miR-522

Upregulated in RA patients

Over-expression increases the levels of TNF-alpha, IL-1-beta, MMP-1, MMP-3, and MMP-13

Inhibition reduces levels of the proinflammatory cytokines and cartilage-destroying MMPs

miR-145-5p

- Over-expression decreases OPG levels and exacerbates bone destruction in mice
- Inhibition leads to higher OPG levels
- Inhibition lead to healthier mice models

Binding Immunoglobulin Protein

- Anti-inflammatory protein found inside and outside of the endoplasmic reticulum
- Displays potent immunomodulatory activity in both mice and humans
- Can down-regulate both immune and inflammatory responses
- Can also inhibit osteoclast differentiation alongside TNF-induced arthritis (current biologics cannot)

Lentiviral Vector Delivery of BiP

- Lentivirus: Viruses with long incubation periods
- BiP was delivered through lentiviral vectors (mBiP/rhuBiP) to see if it could treat arthritis in mice
- In both the low-dose study and the high-dose the vector delayed the clinical progression of CIA in mice
- The vector alters the immunological parameters of the collagen-induced arthritis model and of lymphocytes derived from treated animals

Discussion (Limitations)

- Further research into F8-IL10 (Dekavil) seems to have lagged behind or has yet to reach the public domain
- There is no publicly available research on the use of SP(SP3) antibodies and their use in delivering any sort of anti-rheumatic treatment
- The mechanism by which miR-145 regulates OPG/RANK/RANKL pathway and RA bone erosion is not clear
- Exactly how miR-522 works is also not well understood
- BiP gene therapy for rheumatic disease is still in its infancy

Conclusion

- Many disciplines are invloved towards treating RA
- New fusion proteins will enhance targeted delivery of anti-inflammatory cytokines
- Gene therapy (through the use of mi-RNAs) can be used mediate RA pathogenesis
- BiP therapies can address bone destruction that accompanies RA over the long term
- On top of all that, modern molecular imaging techniques allow for novel methods of study

Any Questions?