Human skin derived-fibroblasts converted into peripheral sensory neurons – a new pain model

- Concern about translational value of rodent physiology to human conditions

- Human nervous system tissue is difficult to obtain

- Easy-to-obtain human skin-derived fibroblasts were reprogrammed into functional classes of neurons, including nociceptors, using a cocktail of lineage-determining transcription factors

- The cells exhibit appropriate morphological and biophysical characteristics and reflect human disease states (i.e. familial dysautonomia)

- This constitutes a major advance in modeling human pain conditions


Using optics to turn pain on and off

**Video snapshot of transdermal optogenetic activation of nociceptors (Iyer and Montgomery)**

- **Optogenetics allows fast, specific neuronal modulation**
  - Recently used to probe transmission of pain signals
  - Avoids expensive, time-consuming development of transgenic mice

- **Virally-mediated optogenetic regulation**
  - **ChR2** (blue light-sensitive, excitatory) or **NpHR** (yellow light-sensitive, inhibitory)

- **ON** in WT mice: activation of ChR2 elicited pain behaviors (*i.e.*, paw licking and flinching)

- **OFF** in neuropathic pain model: activation of NpHR increased withdrawal latency to painful heat

- Valuable tool for *in vivo* study of pain mechanisms
Targeting non-opioid pathways for analgesia: TRPV1 and 5HT3\textsubscript{A} receptors

• TRPV1 function is well described on peripheral terminals of sensory afferents (heat, capsaicin “chili pepper” receptor)

• However, the role of TRPV1 on central terminals is unclear

• Collaborative group from USA and China describe pain-enhancing role of central TRPV1 and 5HT-3\textsubscript{A} receptors in a mouse model of nerve injury-induced hypersensitivity

• Descending serotonergic input from the brain onto central terminals increases TRPV1 activity and pain sensitivity

• These represent novel targets for analgesic drug development

Targeting non-opioid pathways for analgesia: Central A₃ receptors

- Opioid analgesics exhibit undesirable side effects (e.g. tolerance, addiction, abnormal sensation)

- Report from collaborative group from USA and UK, including NIH intramural researchers, describes analgesic efficacy of adenosine subunit A₃ agonists

- Adenosine A₃ activation alleviated pathological pain, with no effect on normal sensation

- Adenosine A₃ activation did not engage endogenous opioid system, and alleviated pain without producing inherent reward

- Existing A₃ agonists exhibit good safety profiles in clinical trials as anti-inflammatory/anti-cancer agents

- Represents promising new approach for pain relief
First evidence of neuroinflammation in brains of chronic pain patients

Evidence for brain glial activation in chronic pain patients

- Glial activation contributes to establishment and maintenance of chronic pain, as shown in animal models
- PET imaging was used to observe brain levels of TSPO, a marker of glial activation
- Patients with chronic low back pain had elevated levels of radioligand binding to TSPO in thalamus, pre- and postcentral gyri, and paracentral lobule
- Thalamic levels of TSPO were negatively correlated with clinical pain and circulating levels of IL-6
- These results are an important step towards developing biomarkers for pain
Racial differences in prescription of opioid analgesics

While awareness of racial disparities in pain care has increased, no trends of improvement have been seen (Meghani et al., 2012 – meta-analysis)

A large national sample of veterans with chronic pain diagnoses across VA hospitals was assessed

Blacks were less likely than white counterparts to receive opioid prescriptions for moderate to high levels of pain (<65yrs)

Racial bias remains an issue for pain care and needs to be addressed

Disparities in Pain Care

Research shows that certain racial/ethnic and socioeconomic groups are more vulnerable to poor pain care and management. This infographic describes some factors that contribute to disparities in pain care.

Bias in Pain Treatment

Across the lifespan and regardless of socioeconomic status, blacks are less likely than whites to receive analgesic medication for pain.\(^1\)

Primary care providers are more likely to underestimate pain intensity in blacks than in other sociodemographic groups.\(^2\)

Compared with white patients, black patients were more likely to have:

- more referrals for substance abuse assessment
- fewer referrals to a pain specialist
- increased drug urine tests

Socioeconomic Status

People with incomes below poverty level are more likely to report pain.\(^1\)

During ER visits, opioids were prescribed more frequently to patients with the highest socioeconomic status.\(^3\)

Language Barriers

Less than 20% of health professionals treating Hispanic pain patients reported Spanish proficiency at an advanced level.\(^7\)

Non-native English speakers may have:

- limited health literacy
- difficulties navigating the healthcare system
- difficulties understanding healthcare providers

Access to Care

Pharmacies located in minority neighborhoods are less likely to carry sufficient prescription analgesics than those located in white neighborhoods.\(^8\)

Impoverished individuals and minorities are more likely to be uninsured or underinsured than non-minorities and people with greater incomes.\(^2\)

Reduced access to health care in general, and specialty care in particular, contributes to pain disparities, with racial and ethnic minorities and the poor having decreased access to care.\(^9\)

Learn More...

The above information points to a need for a multi-disciplinary approach to pain care and treatment, including clinicians’ awareness of implicit bias, data on reducing pain in America (see references) call for a comprehensive palliative health-care strategy for pain, which is currently in progress under the Dept. of Health and Human Services.

Resources for patients with pain:

- Find a doctor
  - http://www.healthfinder.gov
- Patient’s Bill of Rights
- Learn more about chronic pain
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196419/

Resources for providers:

- Cultural & linguistic competency
- National Institutes of Health: Pain Management disparities by Race & Ethnicity
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196419/
- Data from National Institutes of Health

References

Integrative medicine relieves pain and anxiety for cancer inpatients

Effects of Integrative Medicine on Pain and Anxiety Among Oncology Inpatients

Jill R. Johnson, Daniel J. Crespin, Kristen H. Griffin, Michael D. Finch, Jeffery A. Dusek

- Pain is common among cancer patients, and treating cancer-related pain is a challenge for healthcare providers
- Johnson *et al.* studied electronic medical records of 1,833 cancer patients who received integrative medicine therapy
- Patients reported their pain and anxiety levels just before and after the therapy
- Integrative medicine therapy reduced pain and anxiety in hospitalized cancer patients by approximately 50%
- Integrative medicine offers an important tool for healthcare providers to treat pain