Cancer Pain

• What is cancer?
• Role of nervous system in cancer biology
  • Pain generation – neurogenic inflammation
  • Perineural invasion and metastasis
• What is cancer pain?
  • Neuropathic
  • Inflammatory
  • Neither inflammatory or neuropathic
  • Antineoplastic treatment – CIPN, radiation, surgery
• Animal models for human cancer – are they useful?
What is cancer?
From the NCI: Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph system (and via the peripheral nervous system for visceral cancers).
Types of Cancer

- **Carcinoma** - cancer that begins in cells of epithelial origin; e.g., in the skin or in tissues that line or cover internal organs. - Painful

- **Sarcoma** - cancer that begins in cells of mesenchymal origin; e.g., bone, cartilage, fat, muscle, vasculature. These are relatively rare (most bone cancers are not 1º bone cancers). - Painful

- **Leukemia** - cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood. – Not Painful

- **Lymphoma and myeloma** - cancers that begin in the cells of the immune system. -Not Painful

- **Central nervous system cancers** – cancer that begin in the tissue of the brain or spinal cord. Painful in the end
Factors that increase cancer risk

- Chemicals - smoking (50 known carcinogens)
- Diet – high salt (Japan, gastric cancer), high fat (US, colon cancer)
- Infection – usually viral (HPV), Hep B,C, helicobactor
- Radiation – UV, radon -
  - 2007 NCI study – CT scans conducted in 2007 will cause 29K excess cancers cases and 14.5K deaths
- Heredity – BRCA1&2
- Physical agents – asbestos
- Hormones – estrogen
- **AGING – comes with its own pain**
All risk factors lead to genetic changes
Pancreatic ductal adenocarcinoma (PDAC)

In 7 PDAC patients, with 24 different tumors, whole exome sequencing showed:

426 somatic mutations

388 different genes were involved

Geographic mapping of metastatic clones within the primary carcinoma and proposed clonal evolution of Pa08.

Most of these genetic lesions were missense with some silent single base substitutions (no change in coded amino acid)

Conclusion from Yachida et al

• Clonal populations that give rise to metastases are present in primary tumor
• These clones are genetically evolved from original non-metastatic clone
• 10 yrs between original mutation and non-metastatic parental clone
• 5 yrs more before metastasis
• 2yrs more until death
• What does this mean for cancer pain? It may be masked or compensated for until it’s not.
Who gets cancer pain?

• > ten million people are diagnosed with cancer each year. (this does not include skin cancer. By 2020 15M people will be diagnosed each year).

• ~ 30% of adults receiving treatment and 66% with advanced malignant disease experience pain.
  – Head and neck (67-91%)
  – Prostate (56-94%)
  – Uterine (30-90%)
  – Genitourinary (58-90%)
  – Breast (40-89%)
  – Pancreatic (72-85%)

• Are all cancer pains the same?
What is cancer pain?

• Pain caused by the cancer itself (3/4 of patients):
  – Inflammatory pain
  – Neuropathic pain
    » Destruction of endings – e.g. in bone cancer
    » Changes in neuronal environment – pH, tumor derived sensitization (GFs), neuroma formation
    » Perineural invasion

• Pain Cause by treatment (1/4 of patients)
  – Chemotherapeutic Induced Peripheral Neuropathy (CIPN)
  – Radiation induced
  – Surgical pain
  – Opioid paradoxical pain
Inflammatory aspects of cancer pain

- Local and systemic inflammatory response; pro-inflammatory molecules facilitate pain transmission.

- Tumor and associated immune cells release endothelin, cytokines, prostaglandins, TNF-α, growth factors (NGF) and protons, which excite primary afferents.

- Hematopoietic colony-stimulating factors (G-CSF, GM-CSF); IL6/gp130 signaling. (Schweizerhof et al., 2009; Andratsch et al., 2009)
Neuropathic Aspects Cancer Pain

- Invasion of endoneurium and perineurium
- Destruction of nerve fibers
- Distortion of anatomical structures – e.g. periosteum (connective tissue covering bone)
- Sprouting of sensory fibers
- Abnormal interactions between sympathetic and sensory fibers
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Incidence of perineural invasion (%)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer</td>
<td>Up to 100</td>
<td>6,11–13</td>
</tr>
<tr>
<td>Head and neck cancers</td>
<td>Up to 80</td>
<td>2,9,21,23</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2.5–14</td>
<td>9,21,24</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>0.2–10</td>
<td>21</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>75–80</td>
<td>2,9,14–16</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>9–33</td>
<td>2,17–19</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3–38</td>
<td>2,9,20</td>
</tr>
<tr>
<td>Biliary tract cancer</td>
<td>~80</td>
<td>9</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>50–60</td>
<td>2,9,22,25</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>75–85</td>
<td>2,9,26,27</td>
</tr>
</tbody>
</table>

Bapat et al., 2011, Nat. Cancer. Rev. 11:695
Histological section of pancreatic cancer (T) invading the perineural space (N). Immunoreactivity with an anti-CX3CR1 (fractalkine rec) depicts pancreatic tumor cells.

From Marchesi et al. 2010
Even at the precancerous stage in PDAC (PanIN) mice, disseminated pancreatic cells can be found in the sensory ganglia and spinal cord, leading to inflammation in the CNS.
**PanIN stage PDAC pancreas induces activation of spinal cord astrocytes – a feature of both neuropathic and inflammatory pain models**
ATF3 (marker of nerve injury) is expressed at PanIN stage in PDAC mice (typical in neuropathic pain models)
Anatomical changes contributing to PNI and pain – sprouting

Canine prostate injected in mouse femur; tumor cells express GFP. (From Jimenez-Andrade et al. 2010)

Sprouting fibers are both CGRP and NF200 positive – and responsive to anti-NGF (arrow)
Neuroma in mouse model (<26d)
• Sympathetic (TH+) and sensory fibers (CGRP+) are intermixed in periosteal neuromas; 1-2/femur are typical.
• These develop within 21d following injection of cancer cells
• NF 200 staining indicates some of these guys are myelinated
Growth factors/cytokines produced by tumor have autocrine and paracrine functions that drive PNI via sprouting & hypertrophy.
Animal models for cancer/cancer pain

- Until recently most models relied on implantation of cell lines. Death occurred with days-weeks. Not very human-like. (e.g. Mantyh bone cancer)
- Recent models use genetic replication of human disease – still relatively fast (months to year) but includes many/most hallmarks of the disease including precancerous lesions and metastasis. (DePinho, Tuveson pancreatic cancer)
- Carcingens have also been used. (Brian Schmidt, oral cancer)
Pancreatic Ductal Adenocarcinoma (PDAC)

- DePinho/Tuveson – took advantage of most common genetic defect and pair it with KO of tumor suppressor gene
- Depending on p53 (het or homozygous KO) cancer develops 8-21 weeks.
- Mice can live for at least 8 months
- Compare to Mantyh bone cancer – 3wk post tumor cell injection pushes survival limit
These mice express the most common form of the Kras mutation found in human pancreatic ductal adenocarcinoma combined with deletion of p53.

Like human PDAC, mouse tumors exhibit a 9.8 fold increase in NGF mRNA, a 5.2 increase in trkA mRNA and a 6 fold increase in artemin mRNA. (smells like inflammatory pain)
Autonomic Nerve Development Contributes to Prostate Cancer Progression
Claire Magnon et al.
Science 341, (2013);
DOI: 10.1126/science.1236361

Denervation suppresses gastric tumorigenesis
Chun-Mei Zhao et al.
Sci Transl Med 6, 250ra115 (2014);
DOI: 10.1126/scitranslmed.3009569

Basal Cell Carcinoma Preferentially Arises from Stem Cells within Hair Follicle and Mechanosensory Niches
Peterson et al., 2015, Cell Stem Cell 16, 400–412
April 2, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.stem.2015.02.006
Shared features of all 4 cancer studies:
1) Employed naturalistic GEMM
2) Ablated sensory neurons
3) Decrease precancerous and/or cancer lesions

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Models Employed</th>
<th>Nerves Affected by Treatment</th>
<th>Age of Effective Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GEMM</td>
<td>Xeno</td>
<td>Chem</td>
<td>Symp</td>
</tr>
<tr>
<td>Prostate</td>
<td>✔</td>
<td>✔</td>
<td>-</td>
<td>✔</td>
</tr>
<tr>
<td>Stomach</td>
<td>✔</td>
<td>✔</td>
<td>-</td>
<td>✔</td>
</tr>
<tr>
<td>PDAC</td>
<td>✔</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCC</td>
<td>✔</td>
<td>-</td>
<td>-</td>
<td>✔</td>
</tr>
</tbody>
</table>

Saloman et al., TIN, (2016), 39:880
A complex conversation

Released Molecules
- ATP
- SP
- NPY/CGRP
- NE
- NGF
- BDNF
- GDNF
- Artn
- Nrtn
- Protease
- Endothelin
- Protons/AA

Receptors/Channels
- TRP/ASIC
- P2X
- NK-R
- NE-R
- nAchR
- TrkA
- TrKB
- GFRα1
- GFRα2
- GFRα3
- P2Y
- mAchR
- PAR2
- ET-R

Neurogenic Inflammation
Cellular proliferation
Metabolic regulation
CIPN
(Chemotherapy-induce peripheral neuropathy)

- Cancer therapy is often limited by side effects of drugs
  - Nausea
  - Vomiting
  - Cognitive deficits
- CIPN – usually sensory, motor symptoms are less common. Stocking and Glove. Autonomic defects also occur. Sensory defects incl.:
  - Paraesthesia
  - Dysesthesia
  - Proprioceptive deficits
  - Allodynia – mechanical and thermal (cold, most often)
CIPN drugs

- **Taxanes** (e.g. paclitaxel and docetaxel) – alkaloids based on taxol, natural product from bark of Pacific Yew. Stabilized MTs and prevents separation of chromosomes during anaphase.

- **Vinca alkaloids** (e.g. vincristine) – derived from periwinkle, block tubulin from joining MT, blocking cell division.

- **Alkylating agents** (e.g. oxaliplatin, cisplatin (plantinium-based compounds)) alkylated nucleophilic groups modifying DNA and preventing chromosomal duplication.

- **Immunomodulatory** (thalidomide) – blocks angiogenesis via blocking TNFα.

- **Proteosome inhibitor** (Bortezomib) – binds the 26S subunit of proteosome – may block degradation of proapoptotic proteins. Very effective for some multiple myeloma patients.

- **Gemcitabine** - nucleotide analog, block replication, low neuropathy rate (ca. 10%). Go to for visceral cancers – not very effective by itself
CIPN – drugs that keep on giving

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Incidence</th>
<th>Onset time (coasting)(^a)</th>
<th>Duration/recovery after stopping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>40%</td>
<td>From 1 month, at most 3 months (+)</td>
<td>Some recovery in 80% patients over some months/years</td>
<td>Carboplatin less CIPN (10–20%)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Mostly small fibres</td>
<td>Pain common</td>
<td>28% patients symptomatic after some years</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Acute 90% cold induced Chronic 30%</td>
<td>Acute occurs within an hour</td>
<td>More severe less recovery</td>
<td>Chronic CIPN similar to cisplatin 30% CIPN at 2 years</td>
</tr>
<tr>
<td>Vincristine</td>
<td>30–40%</td>
<td>Within 3 months (+)</td>
<td>Acute 2–3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20% limited recovery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In most, some recovery after 3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More severe, less and slower recovery</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30–50%</td>
<td>Maybe after single dose, &gt;50% after second dose (+)</td>
<td>75% some recovery after 6 months</td>
<td>Less common now due to changed dosing</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Most sensory modalities affected</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIPN, chemotherapy-induced peripheral neuropathy. Data taken from [6,35**,36,39].

\(^{a}\) (+) denotes presence of coasting.
CIPN is shares features with other peripheral neuropathies

- Clinical symptoms:
  - Bilateral sensory disturbance in hands and feet marked by:
  - Numbness
  - ‘Pins-and-needles’ sensation
  - Burning sensation
  - Hyperalgesia (hypersensitivity to noxious stimuli)
  - Alloodynia (pain sensation as a result of normally non-noxious mechanical stimuli)

- Preclinical and clinical markers:
  - ↓ Epidermal nerve fibre density
  - ↑ Spontaneous discharge in primary afferent sensory neurons

Bennett, G. J. et al. (2014) Mitotoxicity in distal symmetrical sensory peripheral neuropathies
Nat. Rev. Neurol. doi:10.1038/nrneurol.2014.77
CIPN - MT dysfunction

- Canonical explanation – Chemo disrupts afferent fiber microtubules (MT)
- But – in animal models pain is not always accompanied by MT damage
- Motor axons often not affected
- Some drugs cause pain without MT damage (e.g. bortezomib a highly neurotoxic protease inhibitor).
- Oxaliplatin cause pain before any MT damage is seen.
- Colchicine (not a chemo drug), a classic MT disrupter, is painless.
The “tombstones” of CIPN – evidence of neuronal death

Chemotherapy induced peripheral neuropathy - damage is cumulative and multifactorial.

Nodule of Nageotte-remains of neuron and satellite cells. Found in human as well.

Other proposed mechanisms of the development of distal symmetrical sensory peripheral neuropathy (including CIPN)

Bennett, G. J. et al. (2014) Mitotoxicity in distal symmetrical sensory peripheral neuropathies
*Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.77
Bennett group - taxol induced neuropathic pain is due to mitochondrial damage that damages distal endings.

Mechanical sensitivity (allodynia, hyperalgesia) develops.

Saph.nerve and number of microtubules ok.

No ATF3 expression.

Pos control- sciatic cut

Mitochondria in c fiber and myelinated fibers were swollen and vacuolated - effect may be through Ca++ dysregulation.

This milder phenotype compared to the Mantyh study may be due to route of drug delivery – Mantyh (i.v.) – Bennett (i.p.)
Further evidence of mitochondrial dysregulation

Yilmaz 2015, Neurosci, 300:210
Mito # and size are increased; but function is not (see paper)
Conclusions

• Don’t get cancer
• Cancer pain combines the worst aspects of inflammatory and neuropathic pain.
• Sensory (and other peripheral nerves) may not be passive bystanders in tumorigenesis.
• Treatments for cancer pain can have long lasting negative consequences - CIPN
• We can’t wait for a cancer cure before dealing with these pain issues.