Vaccines targeting early non-viral driver genes to prevent cancer

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Non-toxic interventions that prevent cancer development and progression are urgently needed!

- Hormonal agents are approved for breast cancer prevention
  - These have toxicities that dampen enthusiasm among women who are currently healthy
- NSAIDs can prolong development of recurrent intestinal polyps if given for an extensive time period
  - GI bleeding and ulcers are limiting
- Many other agents have failed in chemoprevention trials
- Chemoprevention has not lived up to expectations!
It is time to look toward the immune system for prevention approaches!

- Vaccines and other forms of immunotherapy are targeted therapies that can also specifically kill cancers while sparing normal tissue.
- Immunotherapy induces memory responses that can combat attempts at development and recurrence unlike other therapies.
- Vaccines were among the most important advances in medicine in the 20th century preventing many deadly infections.
- The immune system can target cancer proteins using mechanisms similar to how it recognizes and kills virally infected cells.
How can immune based interventions prevent non-virus associated cancers?

- Target the earliest genetic alterations in a cancer
- Early inflammatory changes must also be targeted because inflammation occurs with the earliest genetic changes
- GEMMS have revealed that early inflammatory changes are directly linked to genetic alterations that initiate cancer development and cause cancer progression
- Elucidate the earliest inflammatory changes within a developing tumor that facilitate cancer development
The inflammatory response in pancreatic cancer is a progressive, dynamic process, interrelated with cancer genetics.

Zheng, Xue, Jaffee, Habtezion, Gastroenterology 2013

Diagram showing the progression from normal to low grade PanIN, high grade PanIN, and PDA, with interrelated factors such as Telomere Shortening, Kras mutation, P16, Cyclin D1, TP53, DPC4, BRCA2, and mesothelin.
Example: Mutated Kras induces early signals such as IL-8 to propagate a procarcinogenic inflammatory response within the TME. IL-8 is an angiogenic growth factor and chemokine for neutrophils, macrophages and mast cells.
Inflammatory cells have divergent roles depending on the context of the microenvironment.

**M1 versus M2 Macrophages**

**Acute inflammation**
- LPS or bacteria
- CXCL9, CXCL10
- CXCR3
- T<sub>H</sub>1 cell
- IFN-γR
- IFN-γ
- IL-12
- IL-1decoyR
- ROI
- Iron uptake
- Metabolism
- IL-12<sup>hi</sup>
- IL-10<sup>lo</sup>
- IL-23<sup>hi</sup>

**Chronic inflammation**
- CCL17, CCL22
- CCR3
- CD163
- CD63
- MR
- GR
- ST2
- IL-4 or IL-13
- IL-4
- Basophil
- Innate lymphoid cell

**Promotion of T<sub>H</sub>1 response**
- Efficient antigen presentation capacity
- Killing of intracellular pathogens
- Tumor destruction and tissue damage

**Promotion of T<sub>H</sub>2 response**
- Encapsulation and clearance of parasites
- Tumor promotion and tissue remodelling
- Immunoregulation
Kras vaccine + regulatory T cell depletion prolongs survival in KPC mice with early stage PanINs

Mice <2 months old PanIN 1

Mice > 2 months old PanIN 2/3
Vaccination with Treg depletion prevents the progression of PanINs from early to late stage PanIN and PDA.

Mice received 2 cycles of therapy starting at 4-6 weeks of age and were sacrificed 1 week after the second treatment cycle.

Cancer
PanIN 3
PanIN 2
PanIN 1
Normal

No treatment | Vaccine only | Treg depletion only | Vaccine with Treg depletion
What will immune mediated cancer prevention look like?

1. Identify young adults at risk for cancer
2. Determine mutations
3. Choose agent that will modify inflammation associated with the genetic alteration pathway
4. Prevent with mutation targeting vaccine + immune modulating agent