Iron Oxide Nanoparticles Inhibit Tumor Growth

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Background: Superparamagnetic Iron Oxide Nanoparticles

- **Ferumoxytol** (Feraheme, Rienso): FDA Approved
  - Core: Carboxymethyl Dextran
  - Coating: 20-30 nm

- **Combidex**: 40 nm
- **Cliavist**: 100 nm
- **Endorem**: 150 nm
- **Supravist**: 30 nm
- **Clariscan**: 20 nm
Applications and Developments in Therapy

The treatment of tumors using targeted SPIO

1. Targeted SPIO bind specifically to the tumor receptor which selectively suppresses tumor growth

2. Targeted SPIO are used for magnetically induced hyperthermia after tumor binding

3. Targeted SPIO are loaded with therapeutic agents (drug targeting) and these accumulate in the target tissue
Background: Superparamagnetic Iron Oxide Nanoparticles

Applications and Developments in Diagnostics and Therapy

- **SPIO in preclinical and experimental application**
  - Molecular imaging

- **SPIO in clinical application**
  - T2/T2* applications: Liver imaging
  - Spleen imaging
  - Lymph node imaging
  - Tumor imaging
  - Bone marrow imaging
  - Imaging of the gastrointestinal tract
  - CNS imaging
  - Characterization of atherosclerotic plaques

- **SPIO conjugation with antibodies and antibody fragments**
  - Tumor imaging
  - Apoptosis imaging
  - Cardiovascular imaging
  - Cell labeling and cell imaging in MRI
  - Transplant diagnostics, imaging of rejection reactions (graft rejection)
  - Inflammation, infection, and adiposity imaging
  - Imaging of multiple sclerosis (MS) and neurodegeneration
  - Metabolic imaging
  - Imaging of enzymatic activity
  - AND...
Objectives

To evaluate the mechanisms that lead to cancer growth inhibition via local injection of iron oxide nanoparticles into early tumor deposits
Immune responses in solid tumors

DeNardo D and Coussens L 2010
Iron Oxides cause M1 polarization

An unrestrained proinflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice

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Uncontrolled macrophage activation is now considered to be a critical event in the pathogenesis of chronic inflammatory diseases such as atherosclerosis, multiple sclerosis, and chronic venous leg ulcers. However, it is still unclear which environmental cues induce persistent activation of macrophages in vivo and how macrophage-derived effector molecules maintain chronic inflammation and affect resident fibroblasts essential for tissue homeostasis and repair. We used a complementary approach studying human subjects with chronic venous leg ulcers, a model disease for macrophage-driven chronic inflammation, while establishing a mouse model closely reflecting its pathogenesis. Here, we have shown that iron overloading of macrophages — as was found to occur in human chronic venous leg ulcers and the mouse model — induced a macrophage population in situ with an unrestrained proinflammatory M1 activation state. Via enhanced TNF-α and hydroxyl radical release, this macrophage population perpetuated inflammation and induced a p16INK4a-dependent senescence.
Hypothesis

Iron oxide nanoparticles initiate a proinflammatory immune response, based on macrophage influx into tumors and M1 polarization.
Methods: *in vivo* studies

2.3 million Cells to the left lower mammary fat pad

100 Micro litter

MMTV PyMT-derived cells

O₂+1.5% Isoflurane

Postpubertal female FVB/n mice
Methods: *in vivo* studies

- **A**: 10mg/kg Ferumoxytol + Cancer Cells
- **B**: 27.92 mg/kg Ferumoxytol + Cancer Cells
- **C**: 10mg/kg Ferumoxtran-10 + Cancer Cells

*Postpubertal female FVB/n mice*

O$_2$+1.5% Isoflurane

2.3 million Cells + **A** or **B** or **C** to the right lower mammary
Iron oxide nanoparticles initiate a proinflammatory immune response, based on macrophage influx into tumors and M1 polarization.

This finding has important implications for diagnostic and theranostic applications of iron oxide nanoparticles.

Iron oxide nanoparticle-delivery to tumors may support M1-activating immunotherapies, such as the upcoming anti-CD47 therapy at Stanford.
Thank you