RUDOLF LUDWIG KARL VIRCHOW (1821-1902)

omnis cellula e cellula

(Balkwill and Mantovani. Inflammation and Cancer: back to Virchow. Lancet 2001)
TAM, INFLAMMATION AND CANCER

- Mantovani A., 1978; Acero et al 1984
- Bottazzi et al Science 1983
- Biswas and Mantovani, Nature Immunol 2010

**Graphs and Images:**

- **Graph 1:** 
  - Title: In Vitro and in vivo
  - X-axis: hours
  - Y-axis: [H]Thymidine uptake (cpm x 10^3)
  - Data points: Control, mF58 + TAM

- **Image 1:** CD68
- **Image 2:** (Bottazzi et al. Science 1983)
- **Image 3:** (Mantovani et al. Immunol Today 1982)
- **Image 4:** (Mantovani et al. Am J Path 2000)
- **Image 5:** (Biswas and Mantovani, Nature Immunol 2010)
The evidence that links cancer and inflammation

- Inflammatory disease increases the risk of cancer (e.g. thyroid, bladder, cervical, ovarian, prostate, oesophageal, gastric, intestinal)
- Non-steroidal inflammatory drugs protect against some cancers (e.g. colon and breast)
- Inflammatory leucocytes, cytokines and chemokines are present in all (?) experimental and human cancers from the earliest stages
- Inflammatory pathways are downstream of oncogenic mutations (e.g. ras, myc, RET/PTC)
- Targeting cytokines, chemokines, key transcription factors of inflammation and inflammatory cells, decreases incidence and spread of cancer (e.g. TNF-α, IL-1β, NF-κB, Stats)
- Adoptive transfer of inflammatory cells, or over-expression of inflammatory cytokines, promotes tumour development

Inflammation and cancer: Two faces of the same coin

- Inflammation as a risk factor for cancer
- The inflammatory microenvironment in cancer unrelated to inflammation
An inflammatory microenvironment

(Mantovani, Sica, Alavena, Balkwill Nature 2008)

(Mantovani Nature 2009; an integration to Douglas Hanahan and Robert A. Weinberg Cell, 2000)
PATHWAYS LEADING TO CCL2 (MCP-1)

Molecular or biological description:
1) Rollins et al PNAS 85, 3738, 1988
2) Bottazzi et al Science 220, 210, 1983
3) Valente et al Am. J. Path 117, 409, 1984

Molecular identification:
1) Rollins et al PNAS 85, 3738, 1988
2) Yoshimura et al J. Exp. Med. 169, 1449, 1989
4) Van Damme...Bertini et al EJI 19, 2367, 1989
5) Bottazzi et al Int J Cancer 45, 795, 1990
Main targets
Neutrophil
B cell
Immature
Mature
mDC
Monocyte
Eosinophil
Basophil
Naive
Memory
Th1
Th2
Treg
pDC
NK cell

Inflammatory (RED), homeostatic (GREEN), mixed (YELLOW)

(Mantovani, Bonecchi, Locati Nature Rev Immunol 2006)
Leukocyte recruitment
CCL2; CCL5; CXCL2; CXCL8

Angiogenesis
CXCL8; CXCL12; CCL2

Diversion/subversion of adaptive immunity
CCL22; CCL17; vMIP1; vMIP2

Invasion and metastasis
CXCR4; CCR7; CCR9; CCR2; CX3CR1

Proliferation and survival
CXCR4; CCR7; HHV8 GPCR

Senescence
CXCR2

(Mantovani, Allavena, Locati and Bonecchi Cytokine Growth Factor Rev 2010)
Skin (cutaneous lymphoma) Intestine (melanoma) Liver (colon, pancreas) Bone (breast, prostate) Brain (ALL leukemia) Intestine (melanoma) Liver (colon, pancreas) Nerves, ganglia (pancreas) HPC niches (CLL, AML leukemia) Lymph nodes (breast, stomach, melanoma) (Mantovani, Allavena, Locati and Bonecchi Cytok Growth Factor Rev 2009)
Atypical chemokine receptors

No conventional signaling (CTX, Ca, MAPK, …)

The “darc side” of the chemokine system

(Mantovani, Bonecchi and Locati, Nature Rev Immunol 2006; CGFR 2010)
**Chemokine decoy receptor D6**

**Binding**

- CCL2
- CCL3L1
- CCL4
- CCL5
- CCL7
- CCL8
- CCL11
- CCL13
- CCL14
- CCL17
- CCL22

**Degradation**

**Expression**

- Placenta
- Skin lymphatic vessels

**Function**

- Placenta
- Skin lymphatic vessels

D6 is expressed in human Kaposi’s sarcoma lesions

(Nebuloni, Vago et al unpublished)
Reduced in vivo growth of D6/KS IMM transfectants

(Savino et al Unpublished)
The yin-yang of macrophage polarization

M1
- intracellular pathogens
- tissue damage
- tumor resistance

M2
- parasite encapsulation
- tissue remodeling
- tumor promotion
- immunoregulation

Macrophage plasticity and polarization in pathology: in vivo veritas

Annual Review Issue - January 2013

INFLAMMATION, WOUND REPAIR & FIBROSIS

Guest Editors:
Eric S. White & Alberto R. Mantovani

Articles already available online at
MACROPHAGE ORCHESTRATION OF METABOLISM

AMINO ACID METABOLISM
L-Arginine, Tryptophan, Cystine-Cystiene

GLUCOSE METABOLISM
Glycolysis, Insulin signalling

Innate immunity
Insulin resistance

Obesity, Diabetes, metabolic syndrome

Immunoregulation
Cancer

LIPID METABOLISM
Arachidonate
Lipoxin, Resolvins, Protectins
Sphingolipids
Fatty acid oxidation

Inflammation/Resolution
Obesity, atherosclerosis

NAD METABOLISM
Intracellular NAD

Inflammation

Cancer

IRON METABOLISM
Iron loading and export

Chronic venous leg ulcer
Hereditary hemochromatosis

Innate immunity
Tissue remodelling

REDOX METABOLISM
Intracellular glutathione

Immunoregulation

Intrinsic metabolic features (M1)

Intrinsic metabolic features (M2)

(Cairo et al Trends Immunol 2011; Biswas and Mantovani, Cell Metabolism 2012, in press)
(Sica and Mantovani, J Clin Inv, 2012)
Interplay between tumour-associated macrophages and cancer cells in established tumours

Postulated interactions between immune and cancer cells at various stages of carcinogenesis and progression

Mantovani A et al, Lancet 2008
SMOULDERING AND POLARIZED MACROPHAGE-DRIVEN INFLAMMATION IN ESTABLISHED NEOPLASIA

Angiogenesis, lymphangiogenesis, Matrix and remodeling
TNF<sup>low</sup>, IL-6, IL-1
M-CSF, VEGF, PIGF, CCL2, CCL3
Chemokines, MMPs
Recruitment/survival
Tumor proliferation, survival, progression
Growth factors (EGF)
Adaptive immunity (Anergy, suppression, Th2 skewing)
Tumor cell
Response to hormones
Resistance to chemotherapy
Proliferation survival
Invasion metastasis
CXCL12

La Mala Educación
Aspirin and cancer protection – Recent literature

Aspirin and NSAID use and lung cancer risk: a pooled analysis in the International Lung Cancer Consortium (ILCOCO)

Valerie A. McCormack · Ray Jeon J. Hung · Darren R. Brenner · Heike Bickboelter · Albert Rosenberger · Joshua E. Museat · Philip Lazarus · Anne Tjoenstaal · Soren Freis · David C. Christiani · Eun-mi Chun · Loic Le Marchand · Gad Bennet · Hairdy S. Bennett · Angelina S. Andrew · Irene Orlov · Bernard Park · Paolo Boffetta · Eric J. Duell

Are we ready to recommend aspirin for cancer prevention?

Chan AT, Cook NR.
Division of Gastroenterology, Massachusetts General Hospital, Harvard Medical School, Boston, USA.

Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

Lancet, 2012

Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

Lancet, 2012

Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

Lancet, 2012
Tumor-Associated Macrophages and Survival in Classic Hodgkin’s Lymphoma

Christian Steidl, M.D., Tang Lee, M.Sc., Sohrab P. Shah, Ph.D., Pedro Farinha, M.D., Guangming Han, M.D., Tarun Nayar, M.Sc., Allen Delaney, Ph.D., Steven J. Jones, Ph.D., Javeed Iqbal, Ph.D., Dennis D. Weisenburger, M.D., Martin A. Bast, B.S., Andreas Rosenwald, M.D., Hans-Konrad Muller-Hermelink, M.D., Lisa M. Rimsza, M.D., Elias Campo, M.D., Ph.D., Jan Delabie, M.D., Ph.D., Rita M. Braziel, M.D., James R. Cook, M.D., Ray R. Tubbs, D.O., Elaine S. Jaffe, M.D., Georg Lenz, M.D., Joseph M. Connors, M.D., Louis M. Staudt, M.D., Ph.D., Wing C. Chan, M.D., and Randy D. Gascoyne, M.D.

Toward a Personalized Treatment of Hodgkin’s Disease

Vincent T. DeVita, Jr., M.D., and José Costa, M.D.
Targeting cancer-related inflammation

TRABECTEDIN (ET-743, Yondelis) PharmaMar, Spain

1- Natural product derived from a marine tunicate
2 - Binds the minor groove of DNA, interacts with NFY
3- Effective anti-tumor agent in vivo (phase II and III) in soft tissue sarcomas, ovarian cancer, and breast
4- In 2008 approved by EMEA for 2nd line therapy of Soft Tissue Sarcoma, in 2009 for 2nd line therapy of ovarian cancer in combination with Pegylated Liposomal Doxorubicin
5- Clinical activity characterized by delayed, prolonged responses

(Germano et al Cancer Res 2005; 2010; Cancer Cell, 2013, in press; D’Incalci Mol Cancer Ther 2010)
Trabectedin is selectively cytotoxic for Monocytes and reduces some inflammatory cytokines.

Tumor-associated macrophages but not T cells are decreased after Trabectedin

Germano et al, Cancer Cell 2013 in press)
Role of macrophage depletion in the anti-tumor activity of Trabectedin

A

**MN/MCA1 WT**

**MN/MCA1 RES**

![Graph showing tumor weight over time for MN/MCA1 WT and RES](image)

B

Resistance to Trabectedin

![Graph showing % of PI positive cells and tumor weight over time for MN/MCA1 WT and RES](image)

Germano et al, Cancer Cell 2013 in press)
Tumor macrophages and vessels are reduced in treated STS patients

PRE POST
CD31 vessels
CD163 macrophages
(PRE: biopsy before surgery; POST: tumor sample at surgery, after therapy)

Correlation with clinical response

Blood monocytes
TARGETING TAM IS A KEY COMPONENT OF THE ANTITUMOR ACTIVITY OF TRABECTEDIN

- Trabectedin is preferentially toxic for cells of the monocyte-macrophage lineage. In these cells it activates a TRAIL-R dependent extrinsic pathway of apoptosis,
- TAM depletion is sufficient for the anti-tumor activity of Trabectedin (resistant lines; macrophage rescue)
- First evidence that targeting tumor-promoting TAM is involved in the anti-tumor activity of a clinically approved agent (sarcomas; ovarian carcinoma)
- This finding provides proof of principle for TAM targeting in human cancer treatment and has implications for combination therapy and design

(Germano et al, Cancer Cell 2013 in press)
STRATEGIES TO COUNTERACT THE “MALA EDUCACION” OF TAM

RE-EDUCATION

- IFNγ (eg Allavena et al Int J Cancer 1994), TLR
- CD40 agonist mab (Beatty et al Science 2011)

ELIMINATION

- Blocking recruitment and survival (eg anti-CCL2, Qian et al Nature 2011; CSF-1R)
- Elimination (eg Trabectedin, Cancer Cell 2013, in press)

EMEA-approved for clinical use

Clinical evidence of activity
An inflammatory microenvironment

(Mantovani, Sica, Allavena, Balkwill Nature 2008)

(Mantovani Nature 2009; an integration to Douglas Hanahan and Robert A. Weinberg Cell, 2000)
Emerging Hallmarks of Cancer

- Self-sufficiency in growth signals
- Evading apoptosis
- Insensitivity to anti-growth signals
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential
- An inflammatory microenvironment

Hanahan and Weinberg Cell 2000
Hanahan and Weinberg Cell 2011
Mantovani A. Nature 2009
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