“Inflammasomes” – Redefining the way we understand cancer

Adi Idris, PhD
Host-pathogen biology group
PAPRSB Institute of Health Sciences
Universiti Brunei Darussalam

Cancer - A real health concern in Brunei

'Cancer patients in Brunei are younger'

RABIATUL KAMIT
BELAIT

Sunday, June 24, 2012

WOMEN diagnosed with breast cancer in Brunei are younger compared to breast cancer patients from Western countries, according to an oncology specialist at the National Cancer Centre.

Speaking during the Female Day event at the Brunei Shell Recreational Club (BSRC) in Seria, Dato Seri Laila Jasa Dr Babu Sukumaran told The Brunei Times yesterday that the majority of women diagnosed with breast cancer in Brunei are aged between 40 to 50 years old.

Dato Dr Babu, Oncology Specialist at the National Cancer Centre delivering a talk at the Female Day event in Seria. Picture: BT/ Rabiatul Kamit

Breast cancer leading cause of death among women in Brunei

Posted on October 28, 2013, Monday

BANDAR SERI BEGAWAN: Cancer, heart disease and diabetes are the main causes of death at the global level. Brunei Darussalam faces the same health problems, with cancer being the main cause of death for over a decade now, Borneo Bulletin said.

Evidence of cancer in Brunei

RESEARCH ARTICLE

Cancers of the Young Population in Brunei Darussalam

Ibnu Ayyub Mohammad[1], Mas Rina Wati Bujang[1], Pemasari Upali Telisinghe[2], Muhd Syafiq Abdullah[3], Chee Fui Chong[4], Vui Heng Chong[5]*

RESEARCH ARTICLE

Rising Incidence of Primary Liver Cancer in Brunei Darussalam

Raymond Jih Yeong Chong[1], Mohd Syafiq Abdullah[2], Mohammad Moshaddeque Hossain[1], Pemasari Upali Telisinghe[3], Vui Heng Chong[4]*

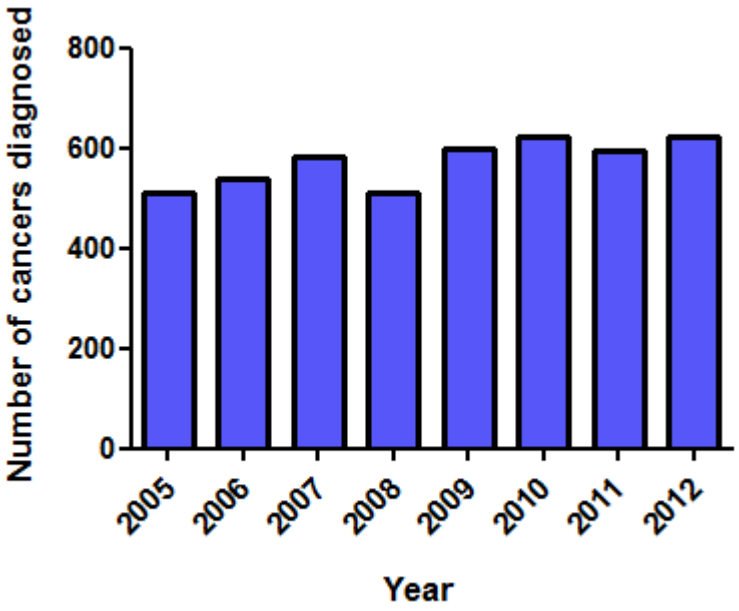
Original Article

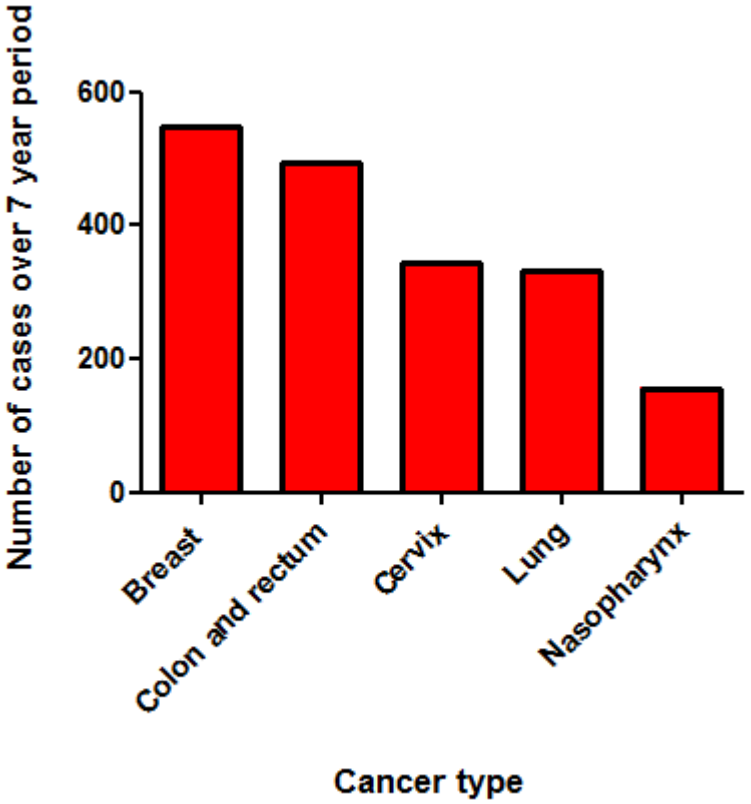
Singapore Med J 2009; 50(11) : 1085

Colorectal cancer: incidence and trend in Brunei Darussalam

Chong V H, Abdullah M S, Telisinghe P U, Jalihal A

Incidence of cancer is rising in Brunei





Courtesy of Dr Kenneth Kok, Director of The Brunei Cancer Centre (TBCC)

HM orders to set up Brunei Cancer Centre

What is cancer?

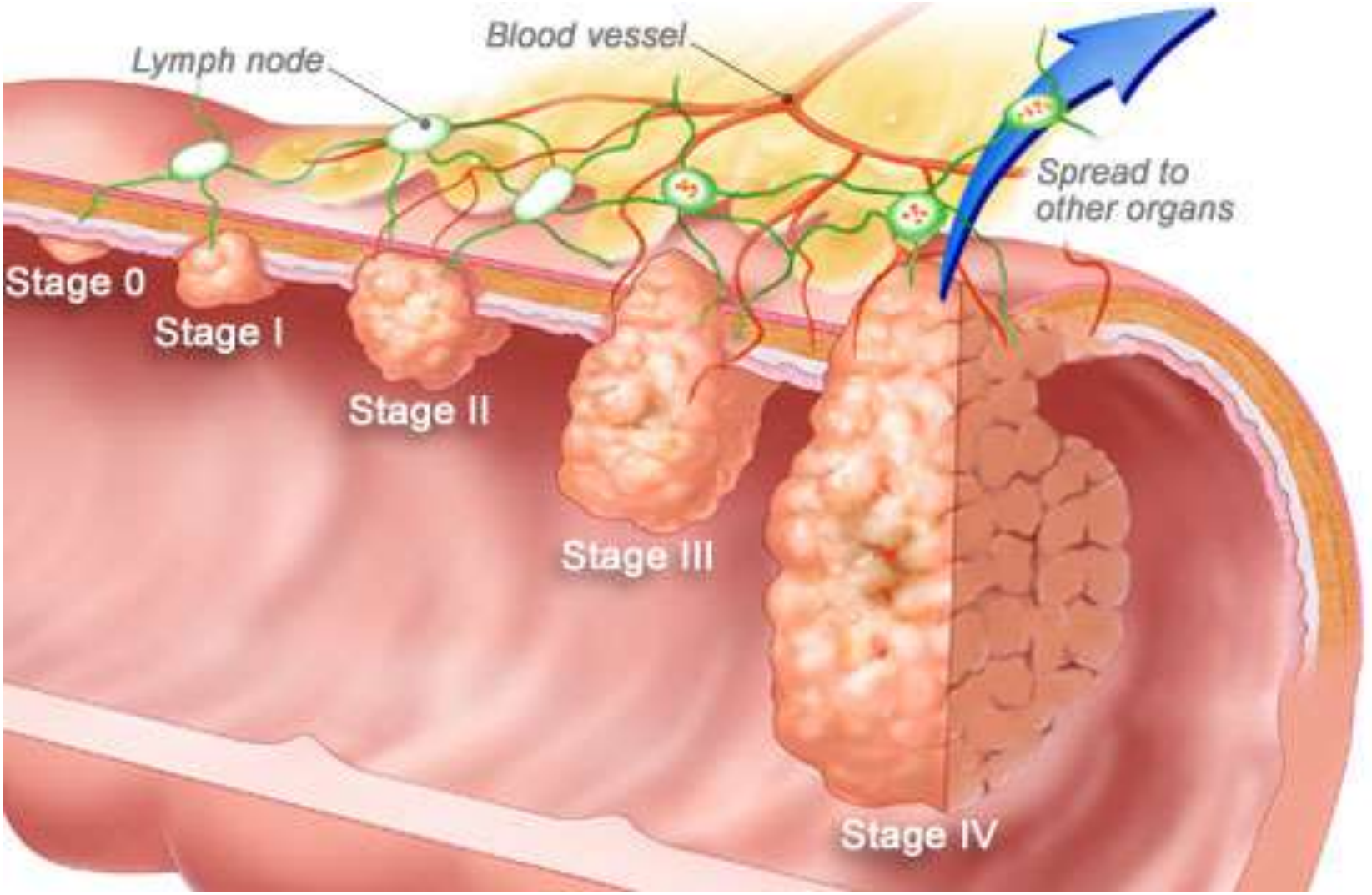
It is a term used for diseases which abnormal cells divide without control and are able to invade other tissues

These dividing cells then form a cell mass known as a "tumor"

Stages in cancer progression

- Stage 0: Presence of some cancerous cells but contained within tissue they developed in – **Non-invasive**
- Stage 1: Cancerous cells are notable (tumor) but still contained
- Stage 2: Tumor is larger than that in stage 1. Has not started to spread in surrounding tissues
- Stage 3: Cancer is much larger and has spread into surrounding tissues. Presence of cancer cells in lymph nodes of the area – **Invasive**
- Stage 4: Cancer has spread from where it started to another body organ - **Secondary or metastatic cancer**

Five critical stages



Genetic mutations are not the “end all”

- Essential to the development of cancer - accumulation of genetic lesions in cells
- However this is not sufficient for tumor growth
- Tumor development – **Both cancer and non-cancer cells**

The non-cancer cells that are responsible for this are the cells of our immune system

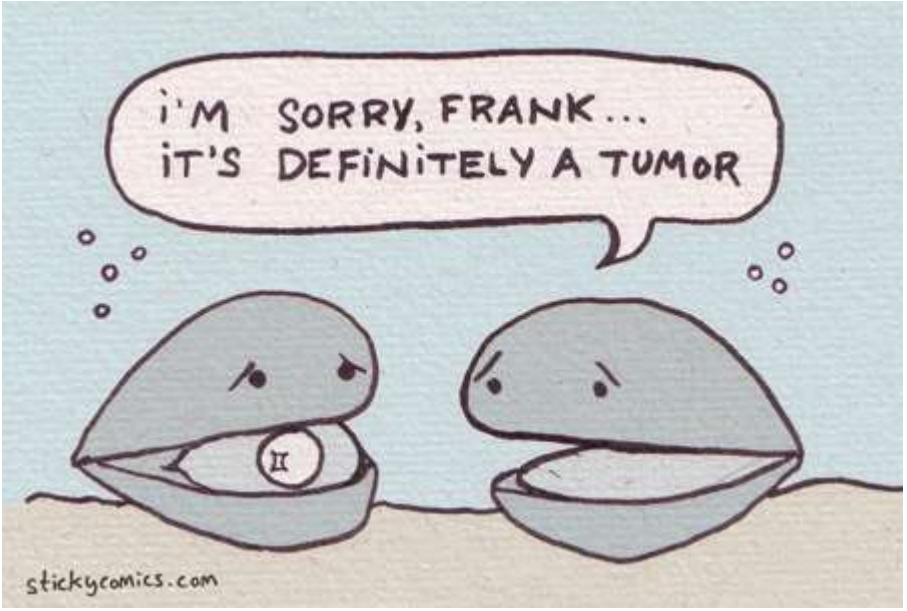
Immune cells are the orchestrators of inflammation

- White blood cells – Cells of our immune system
- Responsible for the production of molecules that cause **inflammation**

White blood cells at home.

What is inflammation?

- Inflammation - a state when our body is on “high alert” usually in response to an infection or……..what appears to be an infection



Cancer and inflammation link…

- The immune system - crucial role in the survival of the tumor
- Inflammatory responses have been long known to be associated with various types of cancers
- These responses play decisive roles at different stages of cancer development

Ever thought why these things contribute to cancer….

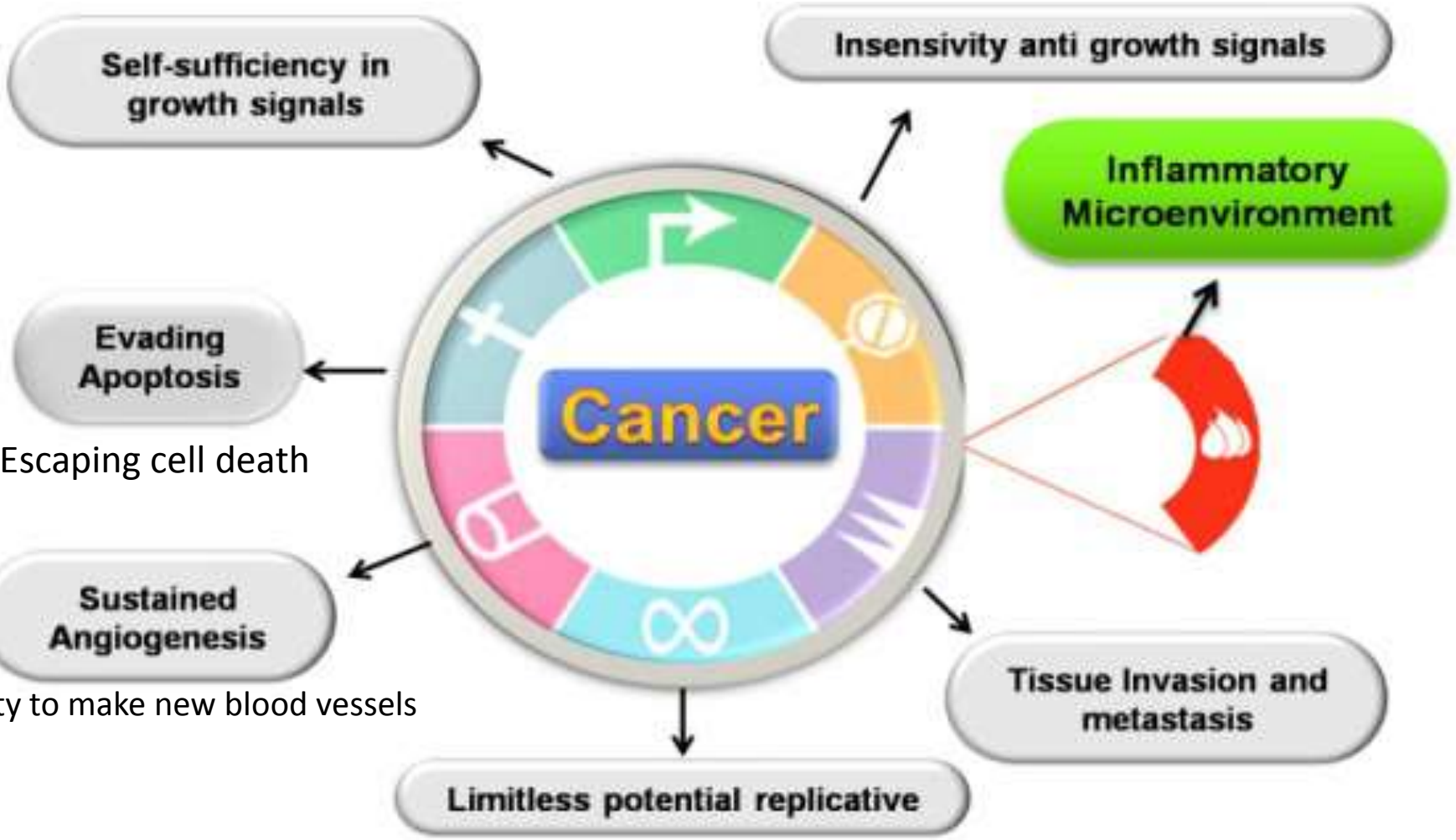
- Many cancer risk factors are associated with inflammation outcomes

Great! So just treat cancer with anti-inflammatory drugs….

"I need an anti-inflammatory."

Unfortunately, it is not that simple

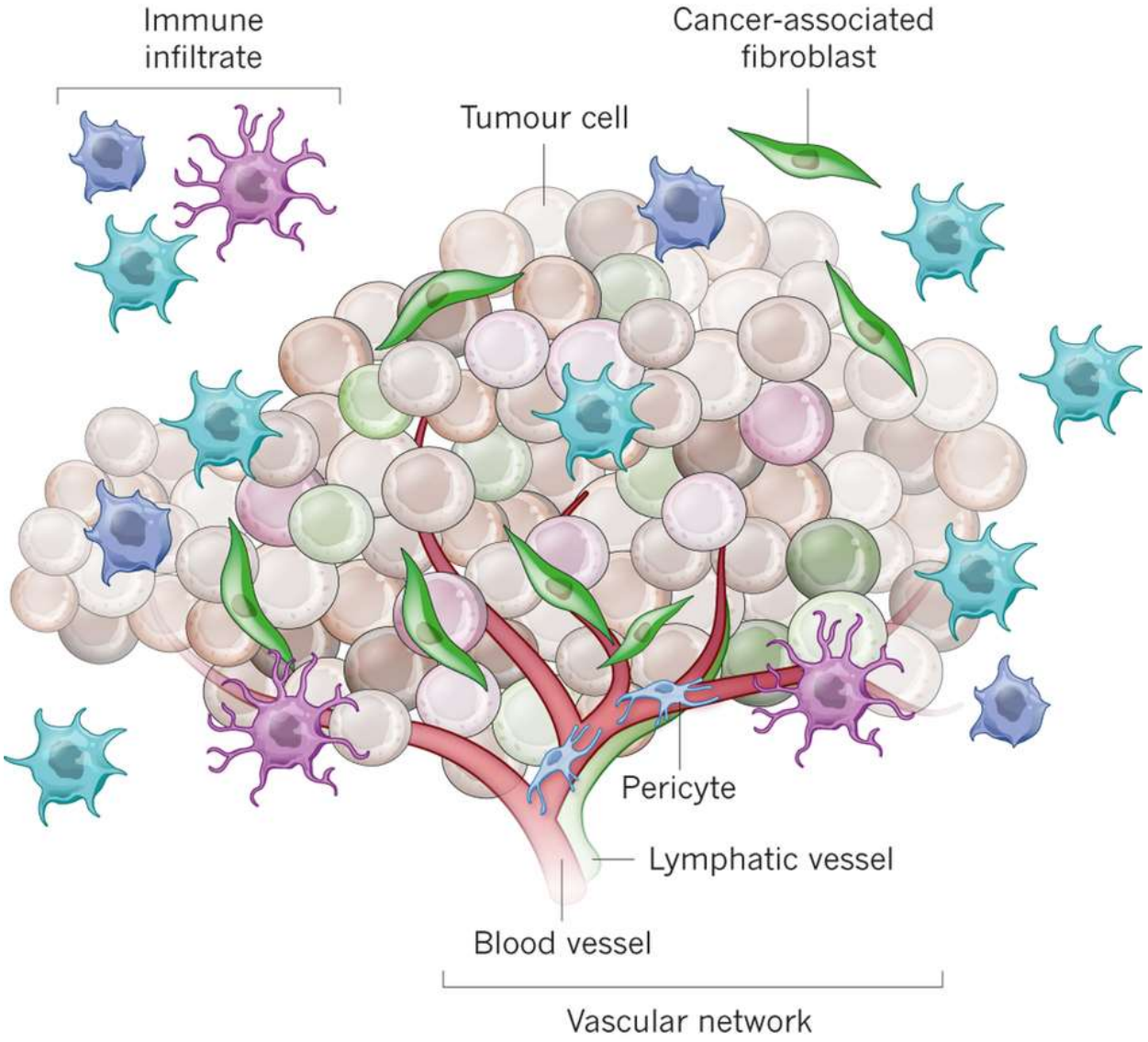
Culprits in cancer



Escaping cell death

Ability to make new blood vessels

“Tumour neighbourhood”



Immune cells are the main orchestrators of inflammation-driven tumor progression

- These cells secrete inflammatory molecules
  - DNA damage
  - Reactive oxidative stress
  - Alters cell division control
  - Genetic “silencing” of anti-cancer genes

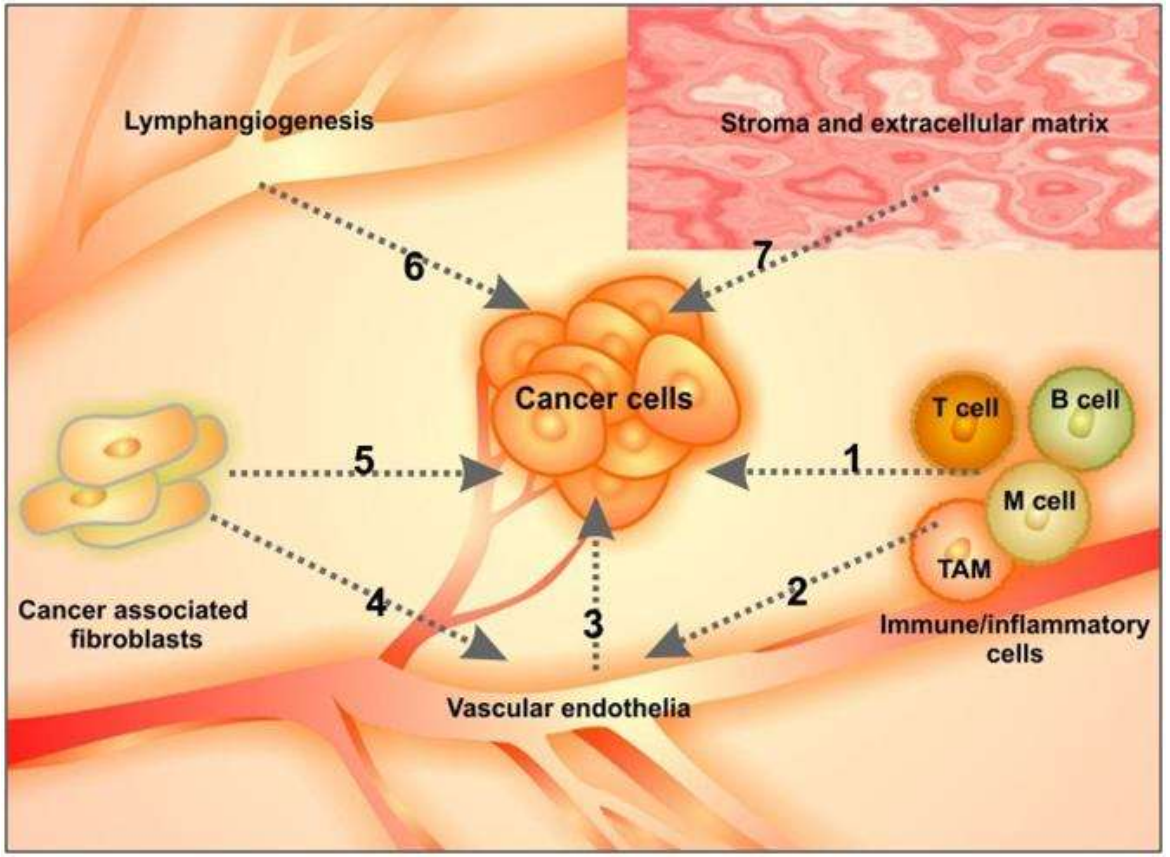
Inflammatory microenvironment

Excessive tumor cells growth and resistance to cell death

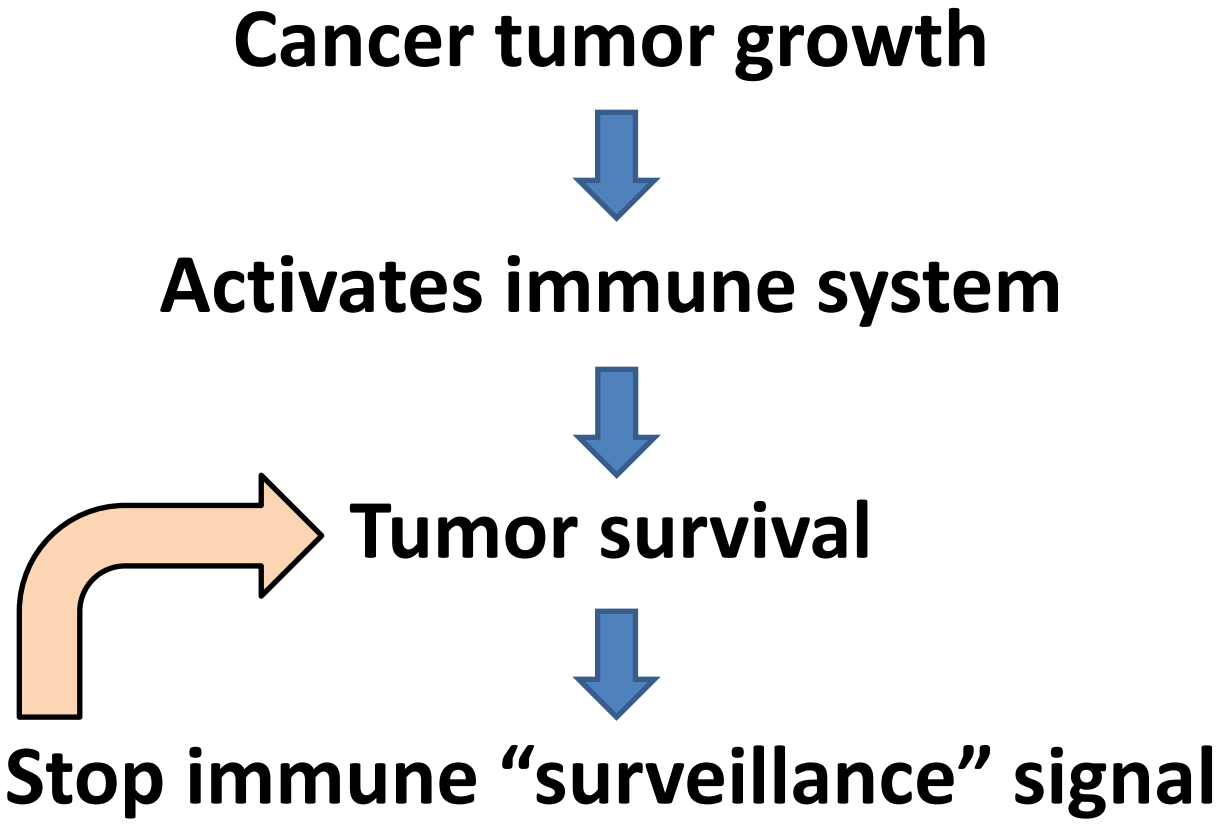
“Tumor maintenance”

What is an inflammatory environment?

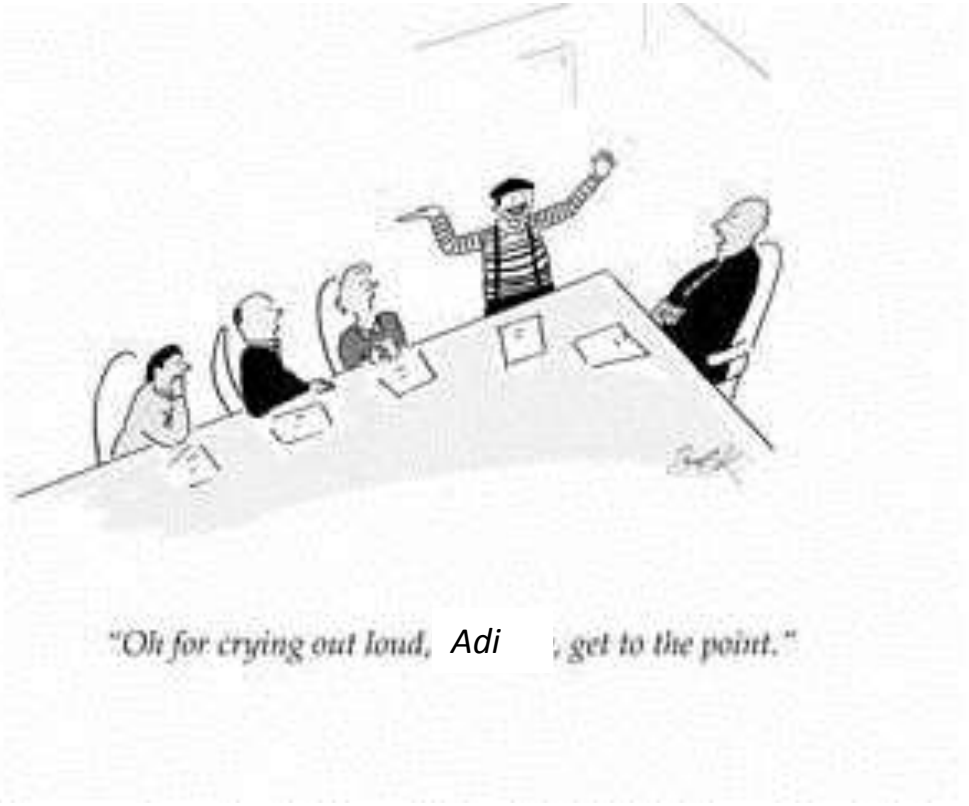
Where cells of the immune system interact with the “tumor neighborhood” to allow the cancer to thrive



Our cells are our own enemy



So what is an inflammasome????



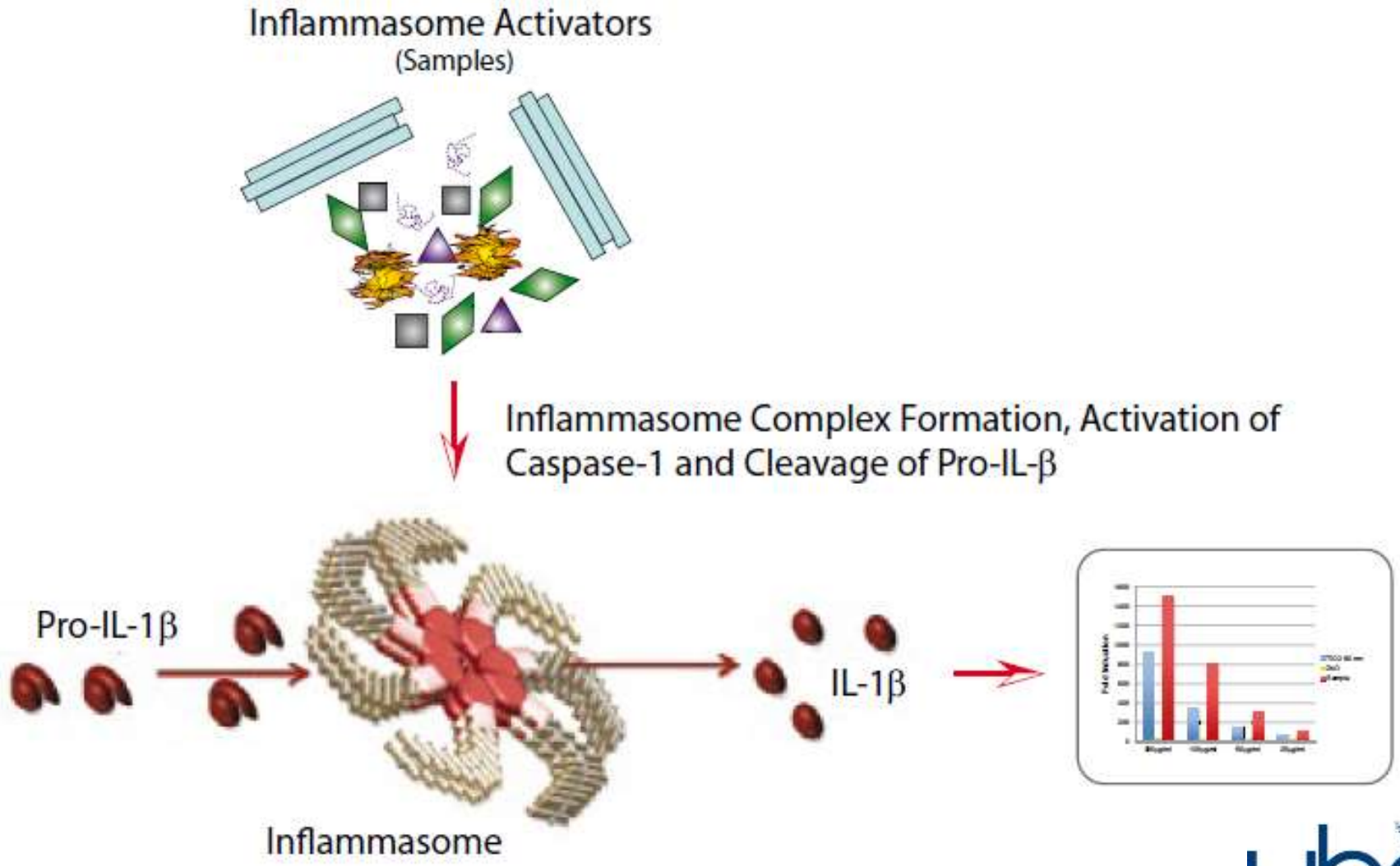
The “inflammasome” – Sentinels of cellular distress

- It is a protein complex that allows the release of “inflammatory molecules” in response to “cellular insults”
  - Environmental pollutants
  - Microbial infection
  - Physiological stress

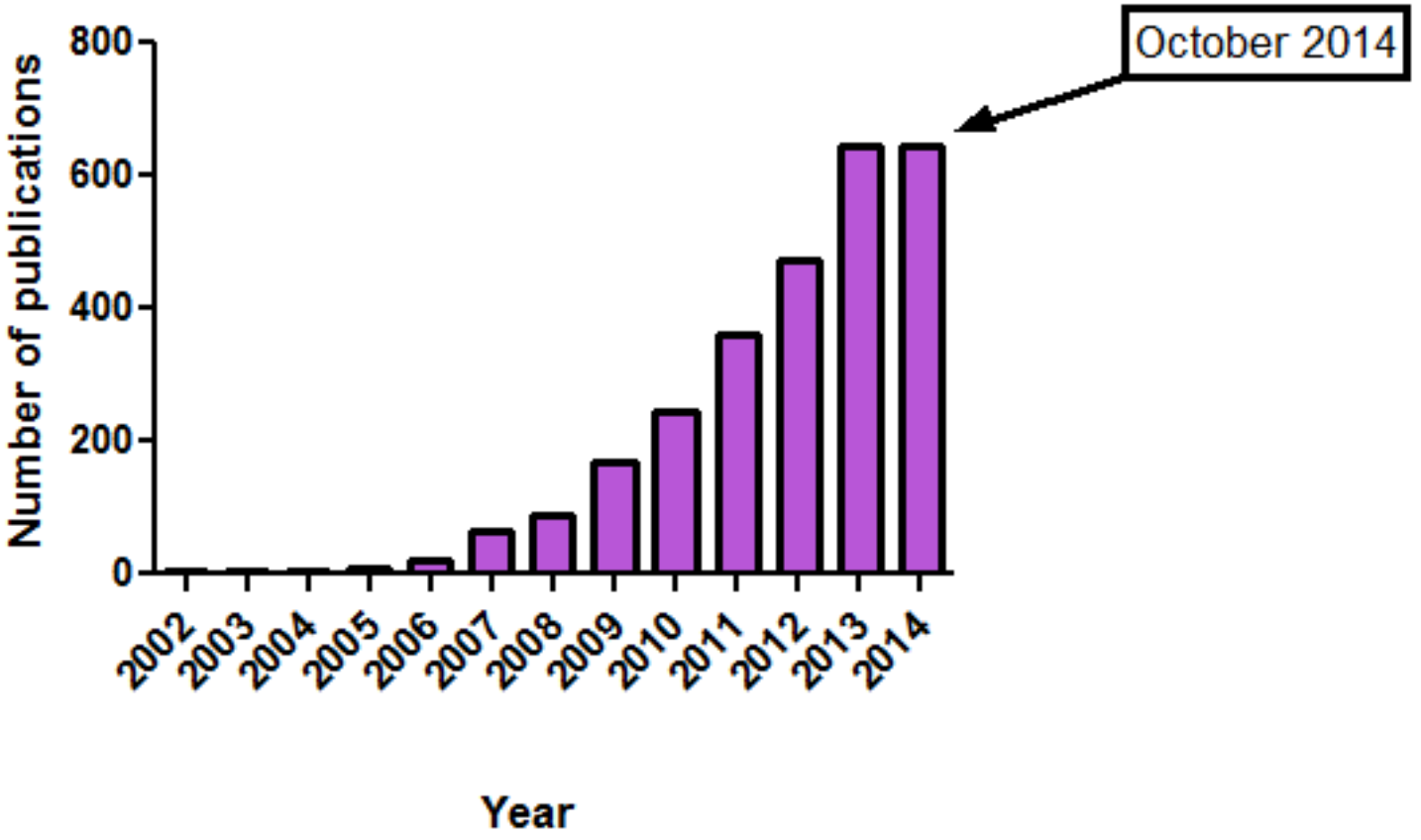
- Important “inflammasome” molecules are interleukin 1 (IL-1) like-proteins

IL-1 proteins are detected at high levels in cancer patients

The inflammasome – In a nutshell



Inflammasome research – On the rise



NCBI PubMed

“Inflammasome” and cancer – An emerging field of research

Associate editor: B. Teicher

Inflammasome: Cancer's friend or foe?☆

Michela Terlizzi [a], Vincenzo Casolaro [b], Aldo Pinto [a], Rosalinda Sorrentino [a,*]

[a] Department of Pharmacy (DIFARMA), University of Salerno, Fisciano 84084, Italy
[b] Department of Medicine and Surgery, University of Salerno, Baronissi 84081, Italy

frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 14 July 2014
doi: 10.3389/fimmu.2014.00327

NOD-like receptors: master regulators of inflammation and cancer

*Mansi Saxena[1] and Garabet Yeretssian[1,2]**

nature immunology

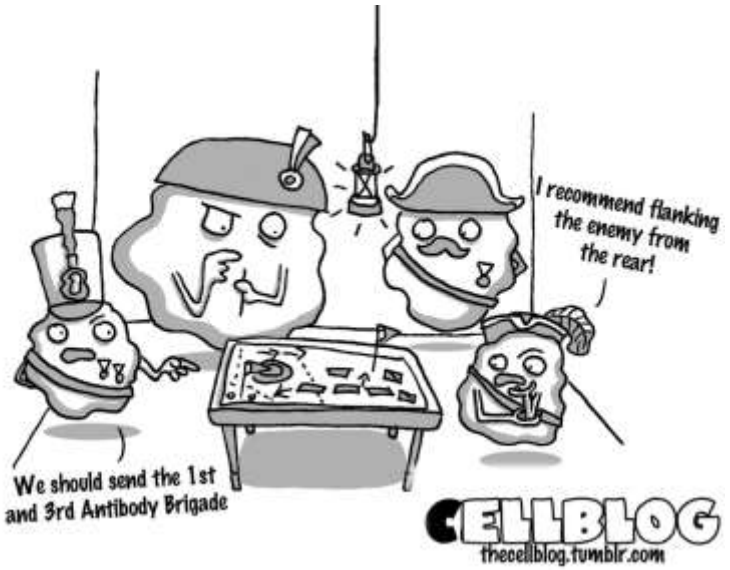
Inflammasomes in carcinogenesis and anticancer immune responses

Laurence Zitvogel[1–4], Oliver Kepp[1,4,5], Lorenzo Galluzzi[1,4,5] & Guido Kroemer[1,5–9]

Creation of an inflammatory microenvironment

- Inflammatory molecules contribute to a chronic inflammatory environment

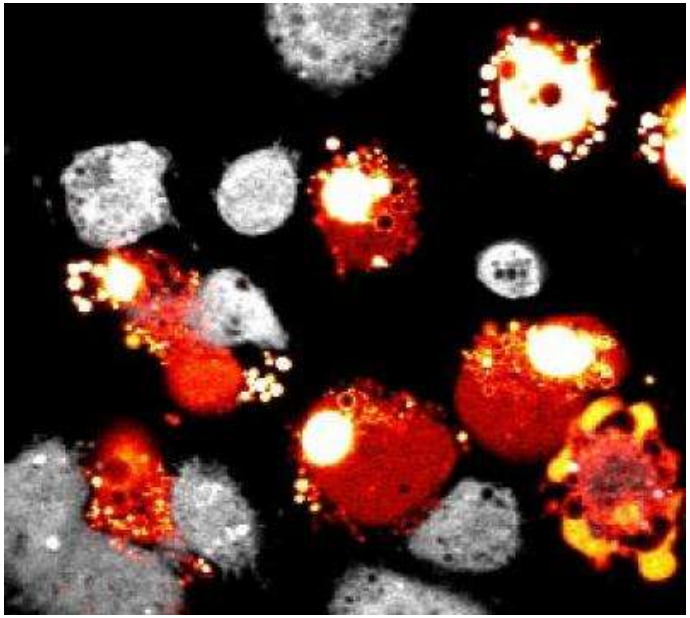
- This environment allows cancer cells to escape or reduce “anti-tumor surveillance”



Inflammasomes also induces a special type of cell death

Pyroptosis

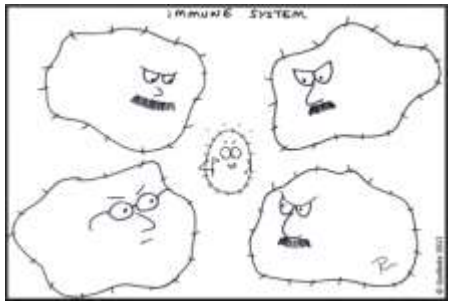
A “messy explosive” cell death – Release of cell contents including inflammatory molecules



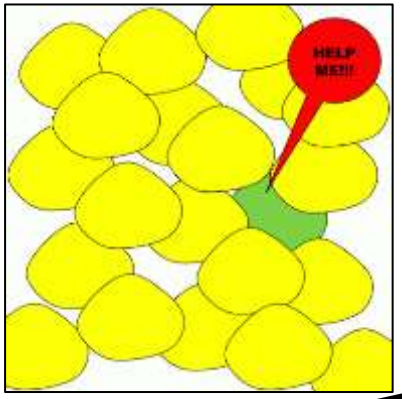
Releases “danger signals” which contribute to the progression/development of cancer

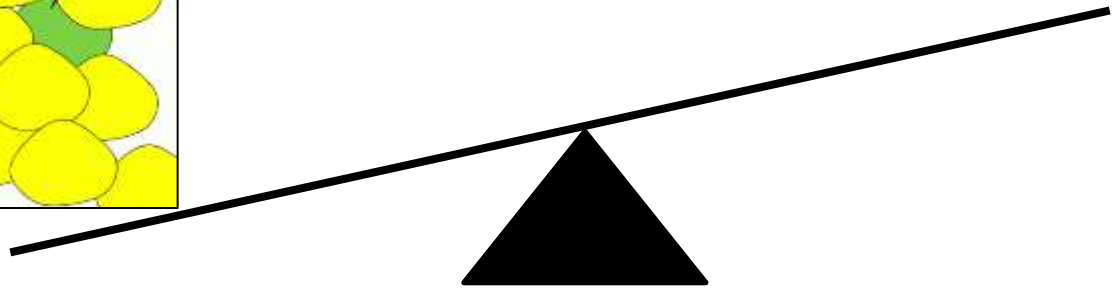
Inflammasomes: Can be good and bad….but mostly bad

Anti-cancer



Pro-cancer





Inflammasome- A double edge sword in cancer progression

- Beneficial: Control excessive inflammation

- Detrimental: Promote tumour survival

Inflammasomes may be a problematic therapeutic target

Protein Cell 2014, 5(1):12–20
DOI 10.1007/s13238-013-0001-4

Protein & Cell

REVIEW

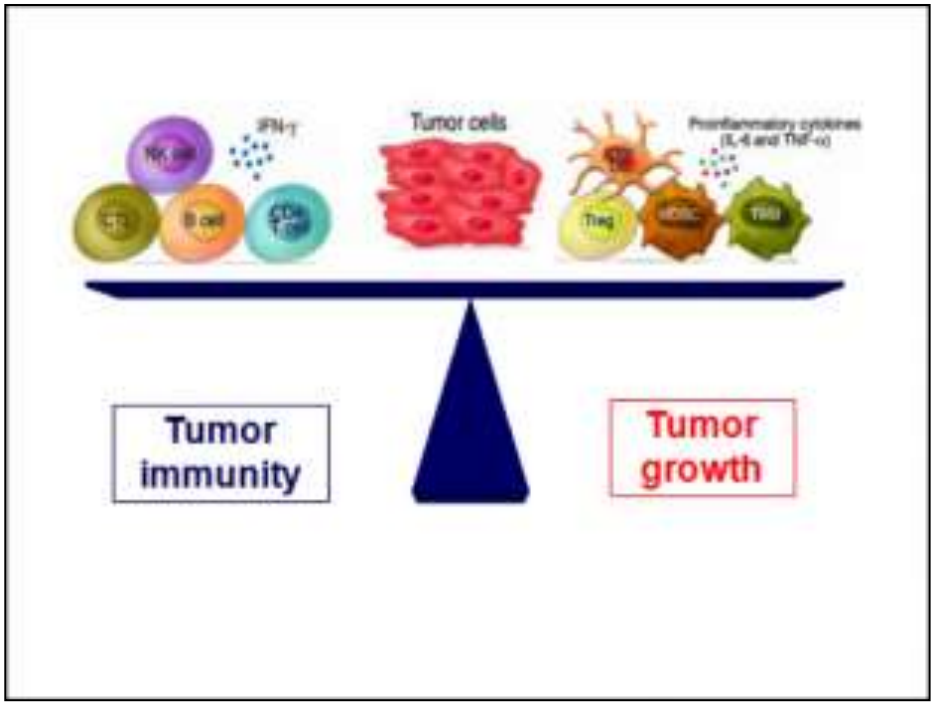
Inflammasomes in cancer: a double-edged sword

Ryan Kolb[1], Guang-Hui Liu[2,3], Ann M. Janowski[4], Fayyaz S. Sutterwala[4,5,6], Weizhou Zhang[1]

The main goal of cancer immunotherapy

1. Activate cells that directly kill the tumor

2. To allow the immune system to “see” the tumor



My previous life

TEAM LEADER
A/Prof Kristen Radford

Generated mice that could make human cells which have anti-cancer potential

FLT3-Ligand Treatment of Humanized Mice Results in the Generation of Large Numbers of CD141$^+$ and CD1c$^+$ Dendritic Cells In Vivo

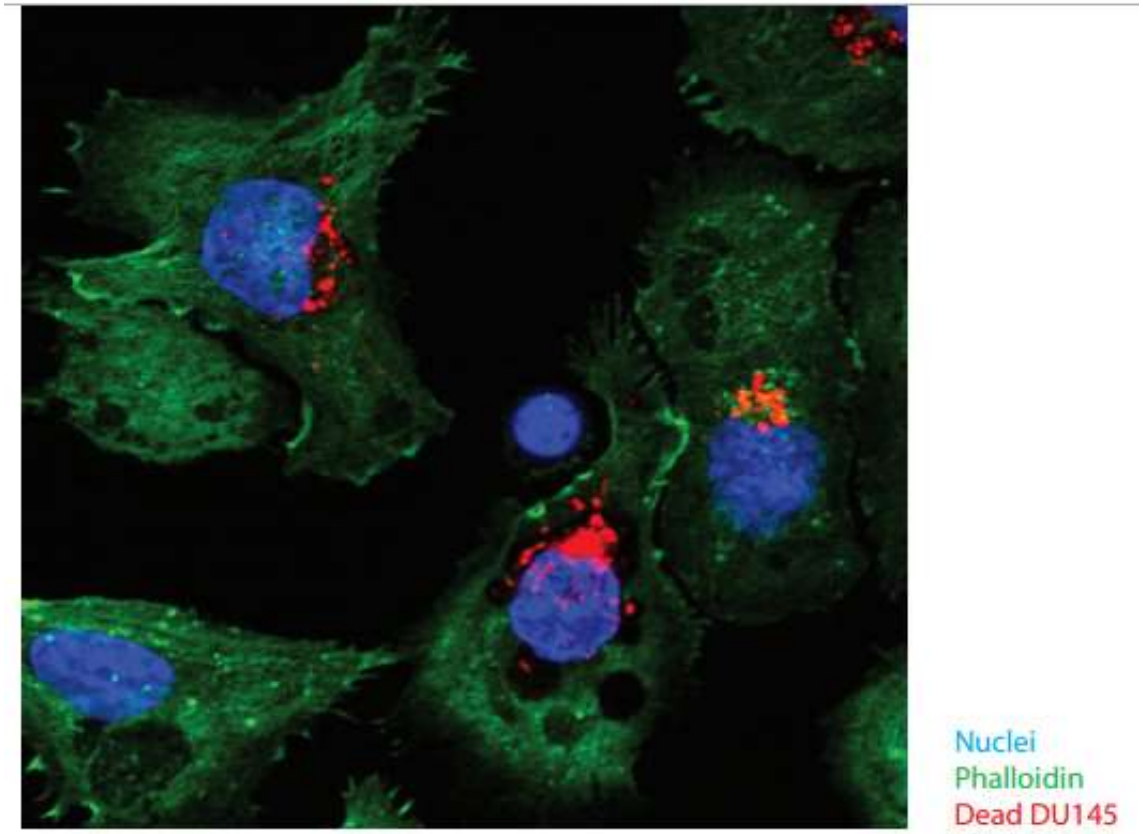
J Immunol 2014 192:1982-1989; published ahead of print January 22, 2014,

Mater Research

TRI
partnering for better health

Ubd

These cells can indeed “eat” dead/dying cells



So is blocking inflammasome "products" therapeutic??

- Several studies support the use of specific inhibitors, antagonists, and monoclonal antibodies against inflammasome products

Cancer Metastasis Rev (2010) 29:317–329
DOI 10.1007/s10555-010-9229-0

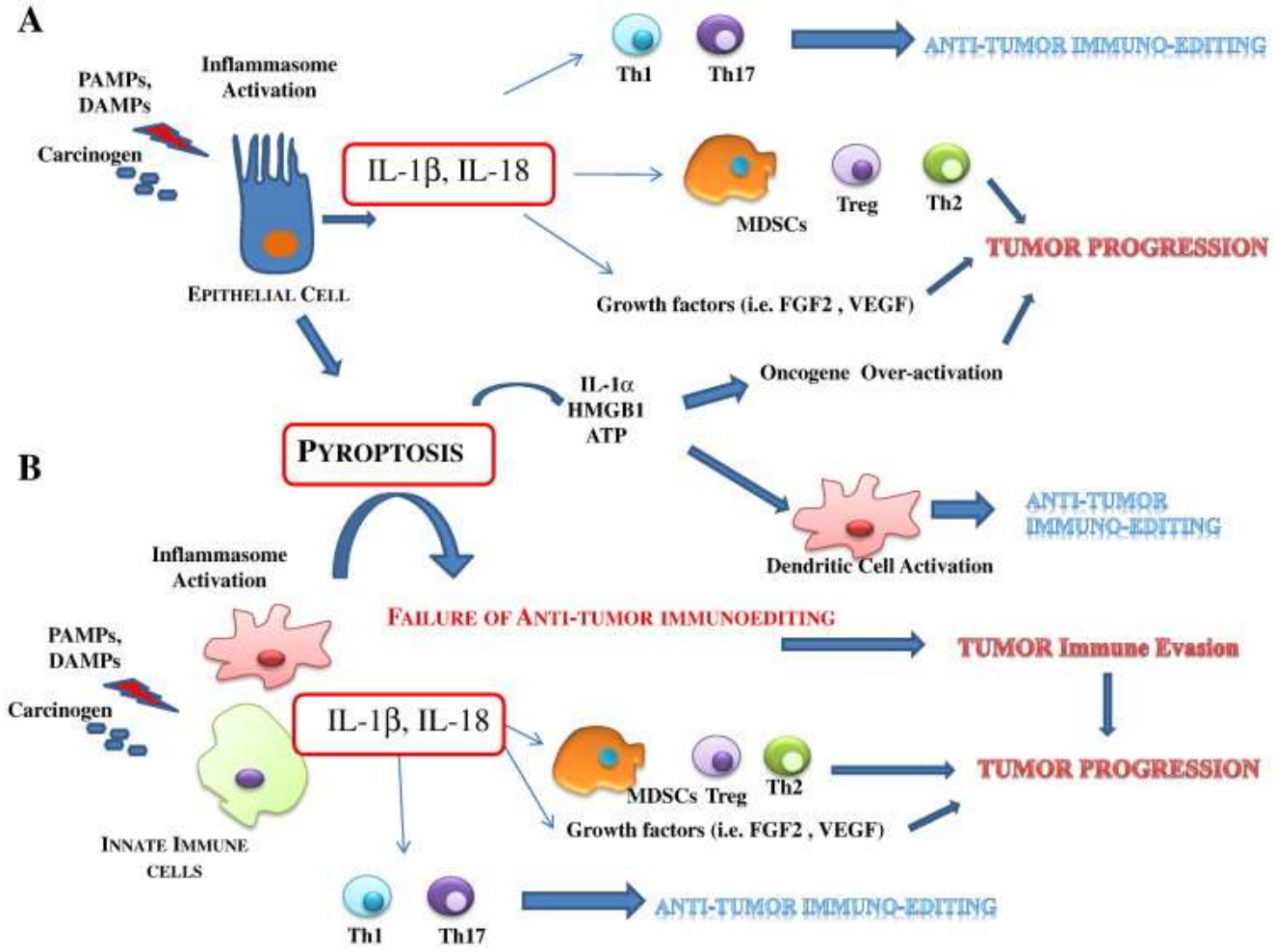
Why not treat human cancer with interleukin-1 blockade?

Charles A. Dinarello

How about killing the tumour itself?

- Targeting the inflammasome
  - it is a desirable target for the tumour but not for the immune cells surrounding it
  - Contents released from dying cells can induce inflammation

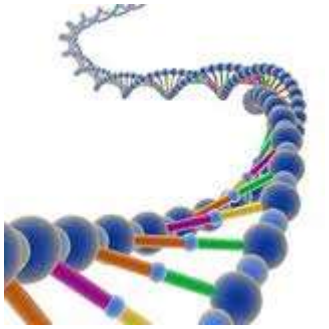
Inflammasome – Cancer's friend or foe?



Pharmacology & Therapeutics, Volume 143, Issue 1, 2014, 24 - 33

My current work

To use synthetic nucleic acids to activate the inflammasome inside cells



Double stranded RNA

Introduce into cells

Activate inflammasome

Inflammation

Cell death

THE KEY IS THE DOSE OF THE NUCLEIC ACID!

Other ongoing cancer-related work I am involved in at the IHS

- Gene microarray expression profile of patient biopsies of all types of cancers in Brunei (Idris A, Mabruk M)

- Investigating the role of potential breast cancer susceptibility genes (Zulkipli I, Idris A, Bujang MR)

- Novel chemotherapeutic drug delivery by solid lipid nanoparticles through the skin (David S, Idris A, Rajabalaya R)

Inflammation: The difference between medicine and poison is the dose

Critical questions

1. How does one program the immune system to specifically drive anti-cancer activities?

2. How can we control “excessive inflammation” in cancer?

3. How can we kill tumor cells without killing cells around the tumor?

4. What is the best way to kill the tumor i.e. how “should” the tumor die?

Host-pathogen biology group

Research sponsor:

2014 UBD Research Grant

Collaborators: