“Inflammasomes” – Redefining the way we understand cancer

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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

Cancers of the Young Population in Brunei Darussalam

Ibnu Ayyub Mohammad¹, Mas Rina Wati Bujang¹, Pemasari Upali Telisinghe², Muhd Syafiq Abdullah³, Chee Fui Chong⁴, Vui Heng Chong⁵⁶

Rising Incidence of Primary Liver Cancer in Brunei Darussalam

Raymond Jih Yeong Chong¹, Mohd Syafiq Abdullah², Mohammad Moshaddeque Hossain¹, Pemasari Upali Telisinghe³, Vui Heng Chong⁴⁵

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
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

- Self-sufficiency in growth signals
- Insensitivity anti growth signals
- Inflammatory Microenvironment
- Evading Apoptosis
- Sustained Angiogenesis
- Tissue Invasion and metastasis
- Limitless potential replicative

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

Cancer tumor growth

Activates immune system

Tumor survival

Stop immune “surveillance” signal
So what is an inflammasome????

“Oi for crying out loud, Adi, get to the point.”
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 Activators (Samples)

Inflammasome Complex Formation, Activation of Caspase-1 and Cleavage of Pro-IL-β

Pro-IL-1β

Inflammasome

IL-1β

Graph showing inflammation levels
Inflammasome research – On the rise

![Graph showing the rise in inflammasome research publications from 2002 to 2014, with a significant increase in October 2014.](image-url)
“Inflammasome” and cancer – An emerging field of research

Associate editor: B. Teicher

Inflammasome: Cancer's friend or foe?

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NOD-like receptors: master regulators of inflammation and cancer

Mansi Saxena1 and Garabet Yeretssian1,2*

nature immunology

Inflammasomes in carcinogenesis and anticancer immune responses

Laurence Zitvogel1-4, Oliver Kepp1,4, Lorenzo Galluzzi1,4,5 & Guido Kroemer1,5-9
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 induce 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

Pro-cancer

Anti-cancer
Inflammasome- A double edge sword in cancer progression

• Beneficial: Control excessive inflammation

• Detrimental: Promote tumour survival

Inflammasomes may be a problematic therapeutic target
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

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.
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

When you see a claim that a common drug or vitamin “kills cancer cells in a petri dish,”

keep in mind:

so does a handgun.
Inflammasome – Cancer’s friend or foe?

A

- PAMPs, DAMPs
- Inflammasome Activation
- Carcinogen
- Epithelial Cell

IL-1β, IL-18

Th1, Th17

ANTI-TUMOR IMMUNO-EDITING

MDSCs, Treg, Th2

TUMOR PROGRESSION

Growth factors (i.e. FGF2, VEGF)

ONCOGENE OVER-ACTIVATION

IL-1α, HMGB1, ATP

PYROPTOSIS

B

- PAMPs, DAMPs
- Inflammasome Activation
- Carcinogen
- Innate Immune Cells

IL-1β, IL-18

Th1, Th17

ANTI-TUMOR IMMUNO-EDITING

MDSCs Treg Th2

Growth factors (i.e. FGF2, VEGF)

FAILURE OF ANTI-TUMOR IMMUNOEDITING

Dendritic Cell Activation

ANTI-TUMOR IMMUNO-EDITING

TUMOR Immune Evasion

TUMOR PROGRESSION

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

To use synthetic nucleic acids to activate the inflammasome inside cells

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 (Zulkipi 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
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