

## The eleventh Korea–Japan–Germany joint symposium on cancer and ageing research

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Received: 6 February 2013 / Accepted: 6 February 2013 / Published online: 28 February 2013  
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**Keywords** Cancer · Ageing · Angiogenesis · Genomics · Proteomics

### Introduction

The Eleventh Korea–Japan Joint Symposium on Cancer and Ageing Research was held along with the first participation of German Cancer Research Center (DKFZ) on July 5th–6th, 2012, at Gyeongju Hilton Hotel in Gyeongju, Korea. We greatly appreciate the communication between Professor Hirota Fujiki (Tokushima Bunri University) and Professor Otmar Whistler, the director of the DKFZ; three scientists from DKFZ participated in this symposium for the first time. This symposium was expanded from a bi-national to a tri-national joint meeting in this year. Prof. Fujiki delivered an opening address that included a short historical background introduction of this meeting and a remark on his conversation with Prof. Wiestler. Later, Prof. Hellmut Augustin kindly introduced DKFZ and the

organization. Scientists in DKFG are organized into seven divisions depending on research programs covering most of the themes in oncology. Two main bodies, the Management Board and Board of Trustees, play a key role in DKFZ administration.

This symposium included diverse types of studies from individual to a team-based integrative approach, including genomics, proteomics and potential therapeutics. We grouped the symposium presentations depending on their cancer or ageing research theme.

### Plenary lectures, special lectures and a cancer research session

Plenary lecture 2: functional genomics and proteomics in cancer research

Pancreatic adenocarcinoma is one of the most malignant tumours that show a poor prognosis. Even worse, most patients are diagnosed at a late stage. Therefore, early and

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accurate diagnosis of pancreatic cancer is critically required but still remains a great challenge. Dr. Joerg Hoheisel (DKFZ) addressed this issue by affinity-based quantitative proteomic analysis: antibody microarray. The results were compared to those from other analyses, such as epigenetic analysis and DNA microarray. Dr. Hoheisel also introduced a technological development in microRNA diagnosis of blood. It is expected that cumulative data would make it possible to diagnose pancreatic cancer early and to identify potential therapeutic targets in the near future. More promising is that these tools can be easily adapted to analyse other disease entities.

#### Plenary lecture 4: beyond VEGF: status quo and perspectives of anti-angiogenic tumour therapy

Professor Hellmut Augustin (DKFZ) started his talk with several unresolved issues in the field of anti-angiogenesis tumour therapy. The main stream of angiogenesis research and anti-angiogenesis therapy has been focusing on VEGF/VEGFR signalling. Prof. Augustin concentrated on the enigmatic role of ANG-2 in promoting sprouting angiogenesis and inhibiting vascular maturation induced by ANG-1/TIE2 signalling. ANG-2 was pro-angiogenic on TIE-2 negative tip cells, which express large amounts of integrins. Interestingly, the ANG-2 effect in these cells was mediated by activating integrin signalling, as monitored by activation of the downstream effectors, FAK and Rac1, and sprouting angiogenesis. This new discovery forms a solid basis for anti-Ang-2 therapy and thus could facilitate clinical applications in the near future.

#### Plenary lecture 5: role of CD44 in cancer stem cells

Professor Hideyuki Saya (Keio University) has been working on the CD44 adhesion molecule for two decades to understand the molecular mechanism for its role in cancer. His long journey on deciphering the CD44 code almost came to an end with quite surprising but intriguing results. He found that CD44, particularly variant forms of CD44 (CD44v), interacts with  $\alpha$ CT, a cystine transporter, and promotes cystine uptake, which leads to high intracellular GSH levels. These elevated GSH levels protect cancer stem cells from ROS which can be generated in large amounts, particularly in the hypoxic tumour micro-environment. In addition, CD44 enhanced the glycolytic phenotype and shifted metabolic flux to the pentose phosphate pathway. These results elegantly explain, in part, the “Warburg effect”. Finally, his novel findings strongly suggest CD44/ $\alpha$ CT as a potential therapeutic target in diverse types of cancer.

#### Special lecture 1: low cell stiffness as a malignant indicator of progression

A question was raised a long time ago by Professor Haruo Sato and his associates: Is there any relationship between cancer cell rigidity and its metastatic potential? Recent developments in nanotechnological equipment have allowed Dr. Masami Suganuma (Saitama Cancer Center) to answer this question. She measured cell stiffness using atomic force microscopy (AFM) as monitored by Young’s modulus (Pa). Initial studies were performed with the B16-F10 and B16-F1 breast cancer cell lines and were extended to other cancer cell lines. She found that all lung cancer cell lines have significantly lower stiffness than normal cells and that cell stiffness decreased when the cells were transformed. Changes in cell stiffness were also observed depending on the cell cycle phase. Although these results suggest that cell stiffness might represent a discrete feature of cancer cells, a quantitative correlation appears to await further investigation.

#### Special lecture 2: diverse functions of the tumour suppressor TIS21/BTG2 in normal and cancer cells

TIS21/BTG2 is a primary response gene whose expression is regulated by stimulation with TPA or other growth factors. Prof. In Kyung Kim (Ajou University) previously reported the diverse role of TIS21/BTG2 in the cell cycle, cell death, maintenance of HSC proliferation and tumour suppression. This presentation introduced more recent work on the role of TIS21/BTG2 in cancer invasion and migration. She found ROS-mediated invasion and migration of breast cancer and A549 lung cancer cells, and that TIS21/BTG blocked NADPH oxidase (Nox)-dependent ROS generation, presumably by downregulating FAK and Src kinase which function upstream of Rac1-Nox. In addition, TIS21/BTG promotes retinoic acid-induced differentiation of HL-60 cells by downregulating both c-Myc mRNA and its protein stability. This TIS21/BTG2 effect on c-Myc occurred by activating Erk1/2 and inhibiting PI3K/Akt. Taken together, cellular context-dependent pleiotropic effects of TIS21/BTG2 suggest its importance in the maintenance of *in vivo* homeostasis.

#### Session D: tumorigenesis and genomic stability, chaired by Profs. Hidetoshi Tahara and Eui-Ju Yeo

In this session, four speakers presented their interesting results on tumorigenesis and genomic stability. Previous studies have revealed many essential functions of the condensin complex in mitotic chromosome assembly and segregation. One of the current issues of this complex is that the subunit function has not yet been clearly defined.

Dr. Kyungtae Kim (Korean National Cancer Center) sought to identify the function of NCAPG2 subunit and its molecular mechanism. Dr. Kim and her associates found that NCAPG2-defective cells show diverse phenotypes: fuzzy chromosome assembly, a significant increase in aneuploidy and cell division without delay under mitotic stress. These cells also showed additional defects in phosphorylation and localization of spindle checkpoint regulatory proteins at the kinetochore. The results indicated a dual function for NCAPG2 in chromosome condensation and chromosome–microtubule attachment.

TRF1 is a well-known telomeric protein that regulates both length and integrity of telomeres. Dr. Hiroyuki Seimiya (Japanese Foundation for Cancer Research) presented an unexpected novel function of TRF1 in the regulation of chromosome segregation. TRF1 is poly(ADP ribosyl)ated by tankyrase-1, which facilitates proteasomal degradation of TRF1. The finding that forced expression of nuclear tankyrase-1, but not cytoplasmic tankyrase-1, interfered with Aurora A-induced mitotic failure prompted him to examine the possibility that TRF1 might mediate the Aurora A-induced phenotype. Indeed, depletion of TRF1 suppressed Aurora A-induced mitotic failure. Further investigation revealed that Aurora A bound and phosphorylated TRF1. As expected, the unphosphorylatable mutant TRF1 did not mediate the Aurora A-induced phenotype. Based on these results, Dr. Seimiya proposed that TRF1 contributes to proper chromosome segregation.

p21-activated kinase (PAK) is a serine/threonine kinase that regulates a wide range of cellular activities. Professor Eung-Gook Kim (Chungbuk National University) and his laboratory members investigated the PAK4 signalling pathway. Interestingly, PAK4 functioned downstream of protein kinase A. This provoked the idea that PAK4 might be involved in the regulation of the CREB transcription factor. Both CREB transcriptional activity and expression levels were regulated by PAK4 activity. Depleting PAK4 in prostate cancer cell lines made them susceptible to chemotherapeutic drugs, and forced expression of PAK4 into androgen-dependant LNCap-FGC cells made them androgen independent. The results suggested that PAK4 is a potential therapeutic target in prostate cancer progression.

Professor Junho Chung (Seoul National University) has been working for over a decade on translational research involving the development of monoclonal antibodies for therapeutic purposes. In this presentation, he showed us an example of how to modify peptides for a therapeutic application that requires a relatively long half-life in vivo. The conventional PEGylation method requires a peptide-specific optimization process; thus, it is time-consuming. His new idea was to make a hapten-conjugated peptide and then to use an anti-hapten-specific antibody as a peptide

carrier. To test this idea, he first generated a hapten-WKYMVm-NH<sub>2</sub>, a synthetic peptide agonist of the formyl peptide receptor family that is effective for treating sepsis. Injection of this hapten-conjugated peptide with the anti-hapten antibody resulted in a significantly improved in vivo half-life. Easy application of this platform technology to other therapeutic peptides is expected.

## Plenary lectures and a session on ageing and senescence

Plenary lecture 1: serendipity in search of longevity—a trivial drug as an elixir

Prof. Sang Chul Park (Gachon University) has been seeking modalities to promote functional longevity in humans. Two strategies can be considered for this purpose: behavioural correction and biological intervention. An epidemiological finding attracted his attention during a survey at Sorok Island where Hansen's people lived until recently. Why do Hansen's people live longer than ordinary people? To address this question, he hypothesized that their lifelong drug 4,4-diaminodiphenylsulfone (DDS) might extend lifespan. It turned out that DDS had a positive effect on *C. elegans* lifespan. Moreover, structural analysis revealed pyruvate kinase as its target protein in mammals, suggesting that DDS might improve sarcopenic muscle weakness in older people. Thus, DDS holds great promise as an elixir of life.

Plenary lecture 3: genetic risk factors in cancer and ageing

This lecture started with a description of accumulated epidemiological and biological data supporting the close correlation between cancer and ageing. Dr. Daniel Campa (DKFZ) addressed this issue with a genome-wide association study (GWAS). A previous GWAS identified an association between the rs401681 locus and pancreatic cancer risk, which was replicated in a recent study. A recent review on TERT locus polymorphisms and cancer revealed a statistically significant association between the rs2736100 polymorphism and risks for diverse types of cancer, including pancreatic cancer. Surprisingly, both rs4975605 and rs2736100 variations were present in the oldest group. The genetic evidence in this presentation supported that these two phenotypes are closely linked.

Session A: senescence and ageing, chaired by Dr. Hiroyuki Seimiya and Prof. Jeong A Han.

In this session, four speakers presented their interesting results on diverse aspects of ageing and an improvement strategy. Prof. Kyung A Cho (Chonnam University) addressed the specific question of how to improve response

to vaccines which frequently decrease in older people. In contrast to previous studies focusing on Toll-like receptor 4 (TLR4), she paid a great attention to the role of TLR5, which is related to the innate immune response during ageing. Flagellin is a specific agonist of TLR5. Prof. Cho found that aged mice showed a greater protective effect from streptococcus pneumonia infection when vaccinated with a flagellin-linked bacterial epitope. Accumulating evidence supports the role for flagellin as an effective adjuvant in various pathophysiologicals. Thus, it is expected that Prof. Cho's proposal will be helpful to older people who need protection from bacterial infections.

Prof. Hidetoshi Tahara (Hiroshima University) presented a new discovery on the role for miRNAs in the regulation of cellular senescence. Senescence may act as a tumour suppressive mechanism, and his previous study identified miR-22, which represses cancer progression by inducing senescence. Further screening newly identified several senescence-associated (SA) miRNAs. One of the features was that senescent cells show a senescence-associated secretory phenotype (SASP). As expected, miR-22 activated SASP. Exosome-miRNA profiling was performed. In contrast to his expectation, exosomes containing miR-22 were seldom secreted. Although the immunological functions of exosomes have been described for immune cells, their pathophysiological functions in senescent cells await further investigation.

Professor Yeo Eui-Ju (Gachon University) described the positive effects of lysophosphatidic acid (LPA) and/or an adenylate cyclase inhibitor (ACI) on wound healing and tissue regeneration in aged animals. She hypothesized that reactivation of senescent cells in aged animals might explain this phenomenon. She found that LPA and/or ACI stimulated expression of several Wnt signalling-related

stem cell markers, such as  $\beta$ -catenin, TCF-4, c-myc and cyclin D1. Moreover, expression of other stem cell markers such as integrin  $\alpha 6$  and CD34 was up-regulated in response to these chemicals. Therefore, stem cell activation may play a key role in LPA and/or ACI-stimulated wound healing and regeneration.

An intriguing talk on the cause and a potential therapeutic modality for myasthenia gravis was delivered by Professor Yuji Yamanashi (The University of Tokyo). Motor neurons control skeletal muscle contraction, which require proper signal transmission through neuromuscular junctions (NMJ). Thus, defective neuromuscular transmission causes muscular weakness or so-called myasthenia. Dok-7 is considered an adaptor-like protein, but it is actually a cytoplasmic activator of the receptor protein tyrosine kinase (PTK) MuSK, which controls neuromuscular synaptogenesis. Because impaired Dok-7 signalling causes NMJ synaptopathy, Dok-7 has emerged as a potential therapeutic target in myasthenia.

### Short talks and poster presentations

The goals of this symposium have been to practice presentation of their own project in English and to encourage participation of young scientists and graduate students in a scientific discussion in the more intimate environment. Thus, five short talks and 21 poster presentations were allocated to young scientists and graduate students on a wide range of cancer and ageing topics. Their hot discussion in a quiet room in the museum made a truly joyful atmosphere.

**Conflict of interest** Here, I declare no conflict of interest.