Fighting a cold, fighting a tumour

Professor Yasunari Nakamoto

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The Faculty of Medical Sciences at University of Fukui has been providing medical training and research for many years, using their close links to the most advanced treatment hospitals in Fukui Prefecture. Amongst the life-saving treatments being developed are those for hepatocellular carcinoma.

Hepatocellular carcinoma is one of the most common forms of liver cancer, and usually occurs as a secondary disease following a viral infection (by Hepatitis B or Hepatitis C) or in patients with cirrhosis, the liver failure often caused by alcohol abuse. As with many tissue tumours, hepatocellular carcinoma (HCC for short) tends to grow in discrete lumps, known as nodules.

The survival rate for HCC is low, with death usually following 3-6 years after diagnosis. Treatment involves the typical approaches: cutting the tumour out (only an option in 15% of patients), destroying it with locoregional therapies with modalities such as radiofrequency ablation and transarterial chemoembolization (effective, but can only target the known tumours) and liver transplants, (which is very dependent on how far the cancer has spread). Unfortunately, the majority of treatments do not prevent recurrence, in which the cancer revives itself from a few stray cells which were not destroyed and goes on to spread once more throughout the body.

What is needed then is a way to fight cancer at the cellular level, rather than with the broad cut of a surgeon's scalpel. Conveniently, the body has a number of mechanisms designed to fight and kill cell-sized objects, mostly as a way to defend itself from bacterial or viral invasion. Is it possible to recruit our own immune system in the fight against cancer? Going from recent clinical trial results, the answer is yes.

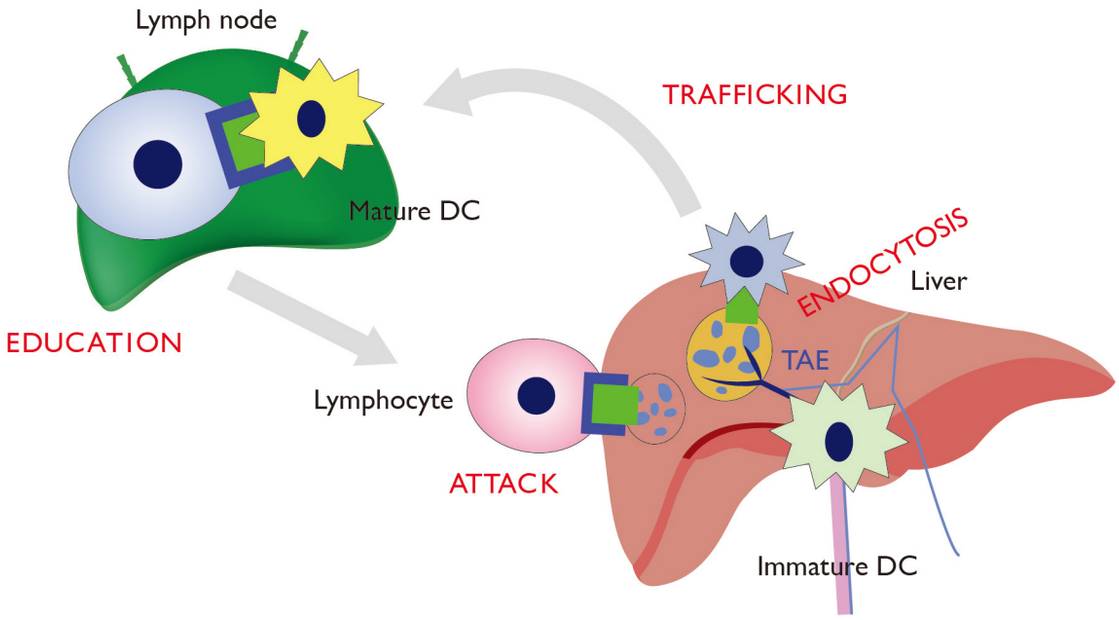
IMMUNOLOGICAL TEENAGERS

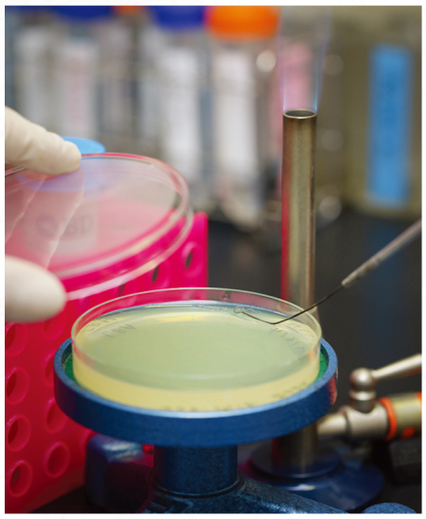
Understanding how this works requires us to delve slightly into the complex world of immunology, a world made up of a number of cell types, all communicating and working together to fight infections. It begins with immature dendritic cells (DCs for short), which spend their youth essentially as most teenagers do, sitting around and eating. Located in areas at risk of infection, such as the skin, lungs, and intestines, they constantly sample the environment by taking up and digesting proteins and other particles from their immediate surrounds. When the immature DC detects evidence of an infection in the vicinity, as determined by the presence of several pathogen-specific chemicals, it begins the process of maturation.

Again like teenagers, maturation involves moving out of home, although in this case the DC merely moves down the hall to the lymph nodes. Here they halt, displaying on the cell surface a snapshot of all the proteins which were in the vicinity when they first began to activate. In effect, this acts as a signature of the infection, a signature which is then displayed to the other immune system cells which reside within the lymph nodes. Through a series of complex interactions, the mature DCs are thus able to activate T-cells, the workhorses of the immune system, inducing them to reproduce and hunt down the invading pathogen. Importantly, because the DC has 'warned' them of the identity of the invader, the targeting of the immune response is extremely specific.

Can our immune system fight cancer? According to recent studies, yes it can.

So how does this process apply to cancer? Through some clever scientific methods it is possible to trick the immune system into believing that the cancer cells are an infection, thus mobilising it into action against the tumour itself. The first stage of this process involves taking a sample of the patient's own blood and purifying a specific type of cell known as a Peripheral Blood Mononuclear Cell (a PBMC for short). It is important that the cells be purified from the patient's own blood, cells from other people would be recognised as 'foreign' by the immune system, and would be rapidly targeted for destruction. PBMCs are able to differentiate, or mature, into a variety of different cell types following chemical treatment, and so these cells are converted in the lab to immature dendritic





cells.

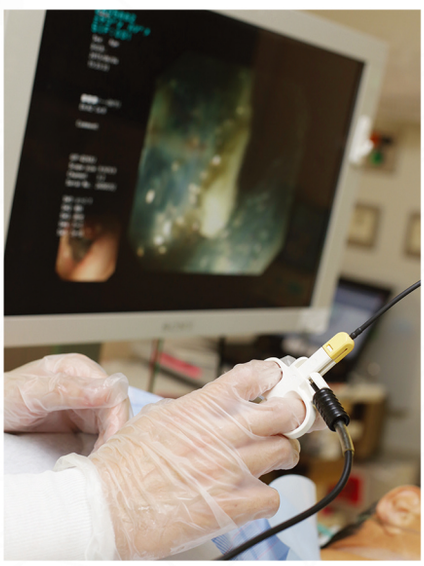
One of the patient's HCC tumour nodules is then injected with a chemical which begins to induce apoptosis, the programmed cell death which leads to the cells essentially committing suicide. This process leaves large amounts of tumour-cell proteins in and amongst the dying cells. At this point the immature dendritic cells are injected into the HCC tumour nodule, along with a chemical which encourages them to begin the process of maturation. The effect of this is that the immature DCs save a 'snapshot' of the tumour environment, including a number of proteins or molecules which are highly indicative of tumour cells. As mentioned earlier, these DCs will then migrate to the lymph nodes and begin to prime the immune system to target and eliminate any cell which expresses these tumour antigens, effectively clearing out the cancer as though it were a normal infection.

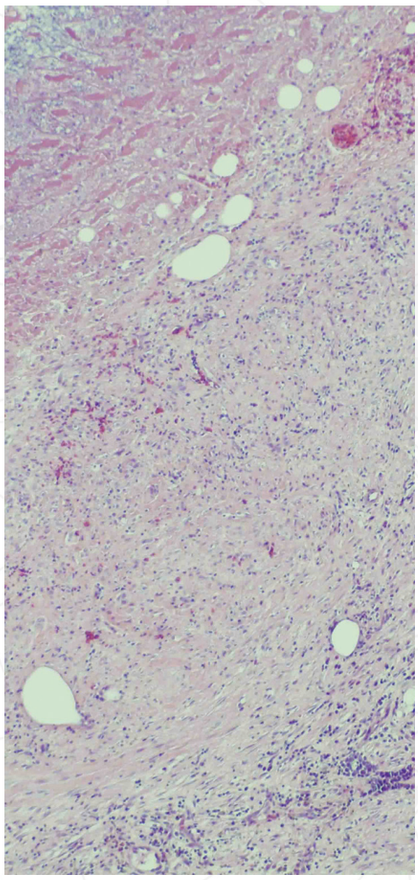
EFFECTIVE ADOLESCENTS

This approach is undoubtedly clever, but how effective is it? Work by researchers such as Professor Yasunari Nakamoto at the University of Fukui, Japan, is beginning to show that it leads to significant improvements in patient survival time. Professor Nakamoto graduated from Kanazawa University in 1989, just as Hepatitis C was being discovered. He spent several years as a postdoc at the prestigious The Scripps Research Institute (TSRI) in California, studying both Hepatitis C and its link to hepatocellular carcinoma. Upon returning to Japan, he commented that "since there were so many patients suffering from HCC in Japan, I decided to use my immunology experience for the treatment of liver cancers. Dendritic cells (DC) were an interesting therapeutic tool for many malignancies, potentially including HCC."

From this initial decision Professor Nakamoto made strong progress, in 2007 he reported on an early stage clinical trial treating 10 patients with hepatocellular carcinoma. PMBCs were taken from each patient, and the process of maturation into DCs took approximately 7 days. On the seventh day the patients were treated by trans-catheter hepatic arterial embolization (TAE), a method for inducing apoptosis in the tumour nodes. This was followed by injection of the freshly prepared, patient-derived DCs into the tumour. Professor Nakamoto's group was able to show that once injected, these cells were able to remain within the region for up to 17 days, collecting a molecular signature of the tumour itself. They then induced the other parts of the patients' immune system to target the tumour cells, developing an immune response against the typical 'tumour antigens' such as Her-2/neu (the target of the ground-breaking anti-cancer drug sold as Herceptin). Most importantly, there were no side effects associated with the treatment, a very important factor when treating already-sick patients.

The group followed up on this success with a new clinical trial, treating thirteen patients





with hepatocellular carcinoma. This trial used a slightly varied method, the cells were extracted and converted into DCs, but this time were treated with a chemical known as OK432 during the conversion process. OK432 is a dried powder made from killed bacteria, Streptococcus pyrogenes to be precise. Because this powder is recognisably 'bacterial', and thus dangerous, it essentially encourages the dendritic cells to 'wake up' and begin the process of maturation, along with several other helpful downstream effects. This new therapeutic method proved to be very successful, while the earlier trial had shown some promise, the use of OK432 led to a significant increase in patient survival. Over half of the patients given standard treatment saw the cancer return within a year (recurrence being a significant problem for hepatocellular carcinoma), however eleven of the 13 DC-treated patients remained cancer-free after one year. The role of the dendritic cells was supported by the observation that the DC-treated patients had higher levels of both immune system signalling proteins and tumour-killing activity. Most importantly, the treatment seemed to be well tolerated by all of the patients. Taken together, this suggests that the DC therapeutic approach is able to significantly extend the life of patients with hepatocellular carcinoma.

ADULTHOOD

These results are very promising, and Professor Nakamoto is confident about the future of these treatments. As he comments, "DC is a very safe and widely applicable therapeutic tool for malignancies. I believe it will become a standard treatment option in combination with current therapies such as trans-catheter hepatic arterial embolization (TAE), in particular for advanced stage cancers. I think the DC therapies can be combined with various treatments, including immune checkpoint inhibitors, for advanced malignancies." Time will tell, naturally, but these initial clinical trials have shown sufficient success that further studies are almost certain to be approved.

Where would he like to take his research after this work is complete? He would like to examine the variability of cancer, as he commented: "During our research into the development of cancer immunotherapies, I noticed that the therapeutic effects were largely different from patient to patient, they were not predictable prior to the treatments." His hope is to extend his work into the field of personalised medicine, essentially using our knowledge of the body at a patient-by-patient level in order to provide the most effective treatment possible.

This process is already quite 'personal', as DC-treatment involves the use of our own cells to fight cancer, but could be improved even further as we determine which tumour cell factors are most important in affecting the chance of the treatment working. Work to this effect is already being conducted, as the Nakamoto group and collaborators attempt to identify a number of chemicals which can substitute for OK432. Although OK432 remains the most effective DC-activator, it is possible that others may be more useful in certain subsets of hepatocellular carcinoma tumours. This type of research is, unfortunately, significantly more complicated to perform, and indeed Professor Nakamoto comments that "there are many questions to be answered in order to solve these problems". Answering these questions and solving these problems, however, remains a goal for many dedicated scientists, with the challenges of cancer heterogeneity and personalised medicine being very hot fields of research indeed. As Professor Nakamoto brings the expertise of his team into play, this field is bound to become hotter still.

Researcher Profile

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After completing his MD at Kanazawa University of Japan, Professor Nakamoto began his long career in research by completing his PhD in Medical Science. After a stint at the prestigious The Scripps Research Institute (TSRI) in California, USA, he returned to Japan and continued climbing the scientific ladder. He is currently the Head of the Second Department of Internal Medicine at the University of Fukui, Japan, with a wide range of research interests.

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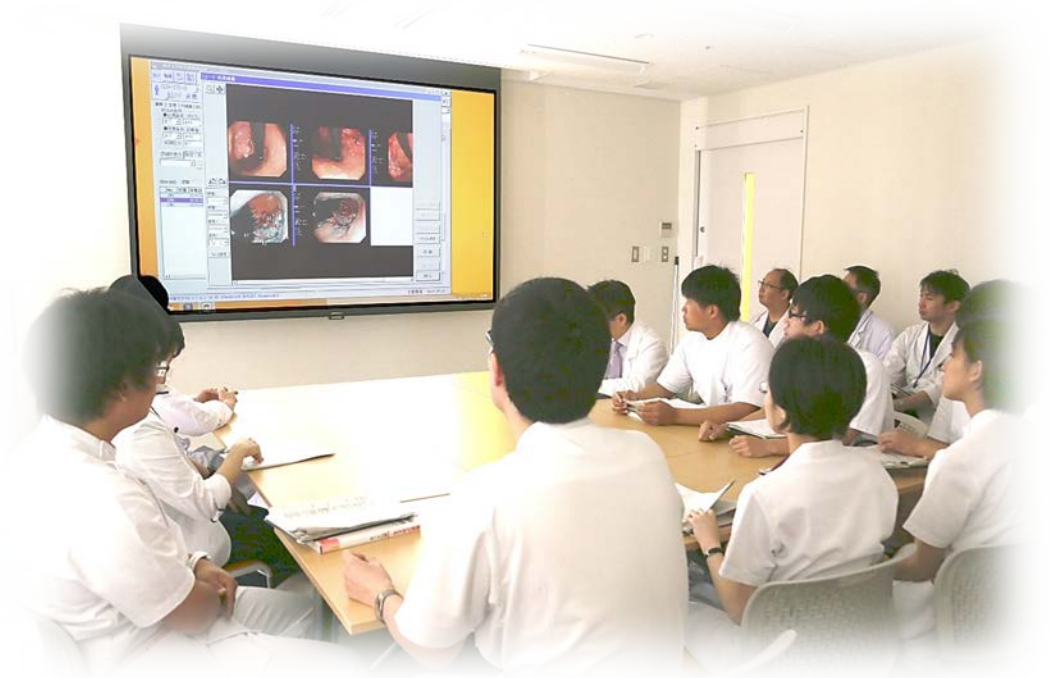

研究内容紹介（Introduction of Research）

・肝臓の慢性炎症が誘導する発がん候補遺伝子におけるドライバー変異の同定（中本安成）

・マイクロキャビティアレイ液体生検技術を用いた肝がん再発超早期診断法の開発（中本安成）

・タウ蛋白オリゴマーが誘導するアルツハイマー病の分子機序の解明 臨床への応用（濱野忠則）

・胃発癌を修飾する食品のエピジェネティクス異常の解析（須藤弘之）

・肝エネルギー代謝に関与する新規転写抑制因子の機能解析と代謝関連肝疾患治療への応用（根本朋幸）

・性差に基づいた胃発癌抑制の試み（大谷昌弘）

・辺縁系脳炎型橋本脳症の臨床像と病態機序の解明（松永晶子）

・Identification of driver mutations in candidate genes for carcinogenesis in chronically inflamed liver (by Yasunari Nakamoto, M.D.,Ph.D.). ・Development of an ultra-early detection method for recurrence of hepatocellular carcinoma using a microcavity array liquid biopsy system (by Yasunari Nakamoto, M.D.,Ph.D.). ・Analysis of pathological role of tau oligomers in Alzheimer's disease (by Tadanori Hamano, M.D., Ph.D.). ・Epigenetic alterations due to Helicobacter pylori infection and diet in gastric carcinogenesis (by Hiroyuki Suto, M.D., Ph.D.). ・Functional analysis and therapeutic applications of a novel transcriptional repressor involved in hepatic energy metabolism. (by Tomoyuki Nemoto, M.D., Ph. D.). ・A protective effect of female hormones on gastric carcinogenesis (by Masahiro Ohtani M.D., Ph.D.). ・Investigation of clinical features and pathogenesis of Hashimoto's encephalopathy in limbic encephalitis.(by Akiko Matsunaga, M.D., Ph.D.)

主な研究業績（Research Achievements）

・Ofuji K, Tada Y, Yoshikawa T, Shimomura M, Yoshimura M, Saito K, Nakamoto Y and Nakatsura T: A peptide antigen derived from EGFR T790M is immunogenic in non-small cell lung cancer. Int. J. Oncol. 46: 497-504, 2014.

・Nemoto T, Matsuda H, Nosaka T, Saito Y, Ozaki Y, Hayama R, Naito T, Takahashi K, Ofuji K, Ohtani M, Hiramatsu K, Suto H, Nakamoto Y: Comparison of hepatic arterial infusion chemotherapy and sorafenib in elderly patients with advanced hepatocellular carcinoma: A case series. Mol. Clin. Oncol. 2: 1028-1034, 2014.

・Muramatsu T, Ikawa M, Yoneda M, Sugimoto K, Matsunaga A, Yamamura O, Hamano T, Okazawa H, Nakamoto Y; Pathophysiological decrease in the regional cerebral bloodflow in Hashimoto's encephalopathy: a multiple-case SPECT study. Eur. Neurol. 72: 13-19, 2014.