RADIATION MEDICINE AND PROTECTION
HARNESSING KNOWLEDGE

A new national key laboratory at Soochow University, focusing on the biological effects and mechanisms of radiation and protection, is becoming a new driving force for the advancement of radiation medicine and protection.

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The use of radiation in medicine since the late 19th century has provided powerful tools for disease diagnosis and treatment, but brings both benefit and risk. Focusing on radiation biology, researchers at the State Key Laboratory of Radiation Medicine and Protection (SKLRMP) in Soochow University are developing innovative strategies to advance radiation medicine and therapy, and to protect against any harmful effects.

Inaugurated in 2018, SKLRMP was built on Soochow University's traditional strengths in radiation research and biomedical sciences. It has united an interdisciplinary team of researchers from the fields of radiology, radiobiology, haematology, clinical medicine, pharmacology, materials science, chemistry, and nuclear sciences. With advanced research platforms and a well-established management system, SKLRMP is making significant impacts on many aspects of medicine and radiobiology.

Revealing mechanisms underlying biological responses to radiation

Effective evaluation of radiation injury and improving cancer radiation therapies require a clear understanding of how tissues respond to ionizing radiation (IR). IR not only impacts the cells it directly targets, but also alters local and systemic tissue microenvironment, which is integral to tissue regeneration and tumour growth.

Focusing on how the tissue micro-environment is modulated by IR, researchers at SKLRMP are studying the response of mesenchymal stem cells (MSCs), a main component in the tissue microenvironment. They found that low-oxygen MSCs exert an anti-inflammatory effect by producing insulin-like growth factor 2 (IGF-2), which is highly expressed upon radiation. The team further revealed the critical role of IGF-2 in instructing macrophages to become anti-inflammatory during their maturation, suggesting an effective route to managing inflammatory diseases.

"Our results show that radiation-induced IGF-2 not only affects the growth of cancer cells, but can also induce immune suppression in the tumour microenvironment," said Yufang Shi, a researcher who led the study. "These have implications for both radiotherapy for cancer and fighting autoimmune diseases."

The SKLRMP team also elucidated the molecular mechanism by which heavy ions effectively kill tumour cells. The key lies in the identification of a long noncoding RNA, *LNC CRYBG3*, which is highly expressed after heavy-ion irradiation. The RNA inhibits tumour growth by disrupting cell division and proliferation. It binds to G-actin, a protein that

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Zhifang Chai (left), renowned radiochemist and a member of the Chinese Academy of Sciences, is discussing with his team members.

can polymerize to form F-actin microfilament, another structural form of actin crucial for cellular functions, and blocks the dynamic interchange between the two actin types. The binding also blocks nuclear localization of MAL protein, inhibiting the expression of genes essential for cellular proliferation and movement, and preventing tumour growth and metastasis. The finding reveals a new pathway for targeting actin cytoskeleton, suggesting a potentially therapeutic anti-tumour strategy.

Advancing diagnostic and therapeutic radiology

Magnetic resonance imaging (MRI) offers a powerful tool for cancer diagnosis. An activatable probe developed at SKLRMP combines improved tumour MRI performance with potential therapeutic effects.

SKLRMP's invention is based on an unsaturated Fe(III)/garlic acid complex, modified on up-conversion nanoparticles. With it, the Fe-O-Fe coupling is broken down in the slightly acid tumour microenvironment, allowing for release of Fe(III), dramatically boosting MRI contrast. The complex also has a unique photo-thermal conversion property, with the released Fe(III) showing excellent tumour therapeutic effects.

Another cancer imaging tool developed by SKLRMP researchers is a ratiometric photoacoustic probe that can be used to quantitatively visualize tumour-related protease activity in vivo. Made of a near-infrared dye and an ester quencher linked by a peptide sequence that can be specifically cleaved by an enzyme called MMP-2, it is designed to detect MMP-2 activity via both fluorescence and photoacoustic imaging. Unexpectedly, through wavelength selective photoacoustic imaging, it presents the capacity to quantify the MMP-2 expression, offering a non-invasive tool for studying the role of tumour-associated proteases in vivo, says Mingyuan Gao, the SKLRMP researcher who led the study.

Radiotherapy is widely used in cancer treatment, but its effect on distant metastasis is poor. To address this challenge, Soochow University researchers have creatively combined radioisotope therapy and immunotherapy. They use a therapeutic radioisotope to destroy local tumours and then stimulate immune responses. Combined with an immune checkpoint inhibitor, this strategy can significantly inhibit tumour metastasis and recurrence. Based on the injection of a hydrogel made up of biocompatible components, this therapy has already proved effective in animal models, shedding light on therapeutic strategies for patients with advanced cancer.

SKLRMP researchers are also combining radiotherapy with CAR-T therapy to improve effectiveness on solid tumours. Based on the finding that an immune checkpoint inhibitor can normalize tumour vessels and reconstruct the tumour microenvironments, the team has developed a new-generation CAR-T therapy which carries an antibody that blocks PD-1, a receptor leading to inactivation of T cells. A clinical trial on a patient with metastatic medullary thyroid cancer showed efficacy in significantly shrinking the tumour, and a biopsy revealed successful homing of CAR-T cells to tumour sites. Given the great potential of radiation to prompt tumour antigen release and enhance PD-L1 expression, the team is examining a combination strategy with CAR-T and radiotherapy.

Improving radioprotection strategies

Improper nuclear waste disposal, nuclear fuel processing and nuclear accidents have resulted in radioactive contamination, threatening human health and the environment. SKLRMP discoveries may help to improve the management of environmental hazards associated with nuclear energy.

To prevent direct discharge of nuclear waste and recover uranium and plutonium resources, removing the radioactive pertechnetate anion ($^{99}TcO_4^-$) from used nuclear fuel is essential. However, given the super acidity, the high ionic strength, and strong radiation field in waste solution, the process is challenging. A cationic network polymer composed of hydrocarbon chains, developed by SKLRMP researchers, exhibits extremely high absorption capacity, ultra-fast uptake kinetics, great resistance to high energy radiation, and excellent acid/base stability. Fully recyclable for multiple uses, the polymer is ideal for nuclear waste partitioning and emergency remediation.

In another study, SKLRMP researchers have developed a decorporation agent for removing uranium from human bodies. Radioactive actinides deposited in bone tissues are extremely difficult to remove. The team has developed a ligand that shows strong affinity and high selectivity towards uranium. Experiments in mice demonstrate its high efficiency in removing uranium from kidneys and bones. Moreover, this ligand exhibits high oral decorporation efficiency, making it attractive for practical use.

SKLRMP researchers have also contributed to radiation monitoring, investigation of high background radiation, treatment of radiation-induced diseases, and more. They are pushing the commercialization of nuclear technologies and their use in medicine. ■

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