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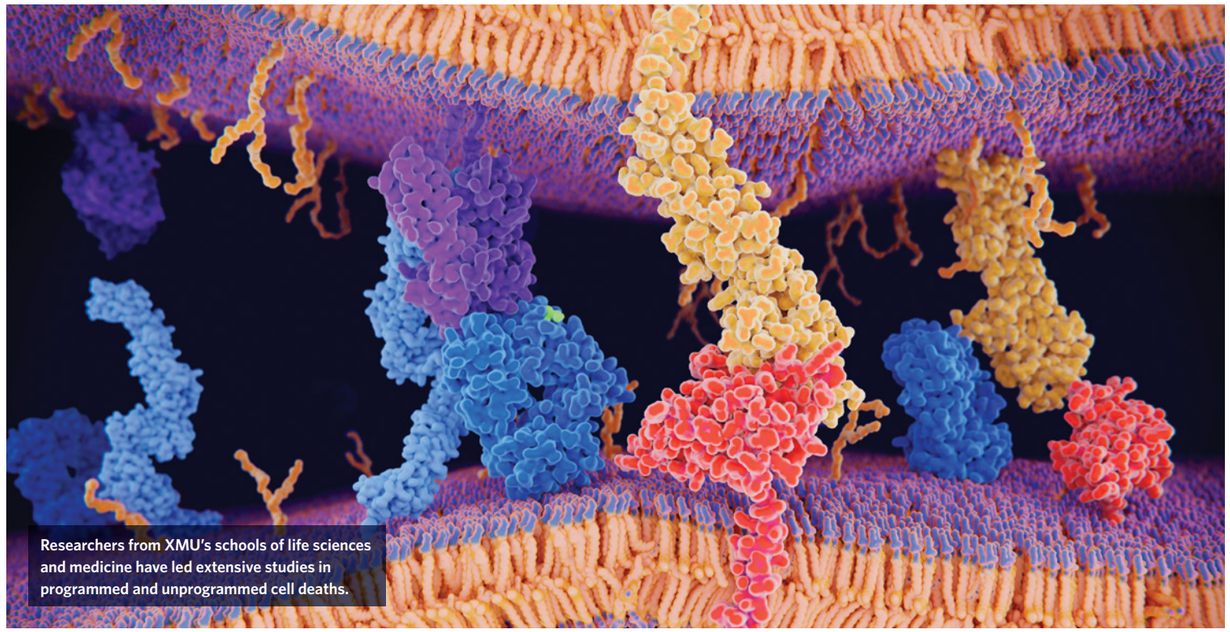
MILESTONES IN BIOMEDICAL ADVANCES

Researchers at XMU are pioneering targeted health innovations in basic science and new therapies.



Researchers from XMU's schools of life sciences and medicine have led extensive studies in programmed and unprogrammed cell deaths.

Advances in basic life sciences and medical research have been driving biomedical innovations and powering healthcare applications. At XMU's schools of life sciences and medicine, researchers have unveiled molecular and cellular mechanisms, shedding light on new treatment strategies.

Uncovering mechanisms of cell death

Cellular necrosis, a form of cell death typically associated with physiological and pathological changes in the body, has long been considered as an unprogrammed accidental process. XMU professor, Jiahuai Han, was among the first to identify RIP3, a protein kinase which controls necrotic cell death and could work as a molecular switch between necrosis and apoptosis, a predefined cell death for maintaining body function.

The discovery, published in *Science* in 2009, has laid the foundation for the concept of necroptosis, a programmed necrotic cell death. Since then, necroptosis has been intensively studied worldwide, and is known to play a role in the initiation and progression of various inflammation-related diseases, from acute pancreatitis and liver cancer to viral infection.

Han's laboratory contributes significantly to elucidating the molecular mechanism of necroptosis. They have found a specific RIP3 phosphatase PPM1b that negatively regulates necroptosis, identified an RSK-mediated caspase-8 inactivation mechanism that promotes necroptosis, and showed molecular details for RIP1/RIP3 phosphorylation and oligomerization, and MLKL translocation to cell membrane.

They also revealed the role of necroptosis *in vivo* in disease models of atherosclerosis, sepsis, and inflammatory bowel disease (IBD). The team is also among the first to identify a protein, GSDMD, as the executioner of pyroptosis, a pro-inflammatory type of cell death. These studies have led to publications in leading journals, and the key regulatory molecules of necroptosis have become important targets of drug development.

Joining XMU in 2014, Wei Mo discovered a novel intrinsic signal of necroptotic cell death. Collaborating with Han, Mo's team found that RNAs of reactive retro-elements in genome can be sensed by the protein, ZBP1, which in turn forms necrosome, a supermolecular complex mediating necroptosis, in intestinal stem cells. This pathway plays a critical role in the pathogenesis of IBD. This finding, published in *Nature* in 2020, suggests a potential treatment strategy for severe IBD by targeting necroptosis of intestinal stem cells.

Mapping molecular routes for diseases

For XMU professor, Shengcai Lin, his team is interested in molecular mechanisms underlying metabolic regulations. Their recent research has been focusing on how AMPK, an enzyme known as an energy sensor in a cell, is activated in response to glucose starvation. The team is also interested in how lipid absorption and synthesis is regulated.

In a study published in *Nature* in 2017, they found that the lysosomal AMPK pathway senses the availability of glucose. They also identified that aldolase, a glycolytic enzyme, works as a sensor of glucose availability, and regulates AMPK. Their work demonstrated that glucose starvation activates AMPK without changing the energy status in the cell or animal tissues, challenging the traditional view that AMPK activation strictly depends on increased AMP levels. This discovery was selected as one of China's top 10 advances in life sciences in 2017.

Based on the signalling pathway, Lin's team has screened chemicals that mimic glucose starvation to trigger AMPK activation. These chemicals may have potential therapeutic benefits from reducing weight, lowering blood glucose level, to suppressing tumour growth. The patented technology has been licensed at 20 million yuan to a biotech company for developing drugs targeting metabolic diseases and cancers.

Further research with implications to drug discovery is led by Dawang Zhou, vice president of XMU and dean of the School of Life Sciences, who focuses on the Hippo signalling pathway, which controls organ size by regulating cell proliferation.

Zhou's team has been investigating how the Hippo pathway regulates the size, development, and regeneration of organs, particularly, the liver, and has uncovered the mechanisms and roles of many Hippo-associated proteins in organ development and cancer.

In a paper published in *Cancer Cell,* they identified that lack of protein kinases MST1 and MST2 (MST1/2), which are central components of the Hippo pathway, will lead to liver enlargement and even liver cancer. They also explained how deficiency of the effector gene, YAP, causes apoptosis and liver failure.

With his colleague, Xianming Deng, the team identified a small-molecule inhibitor targeting MST1/2, which has been proven efficient to promote tissue repair for liver and intestinal damage, and has been successfully licensed.

Zhou has also collaborated with other teams to improve drug delivery using nanotechnology.

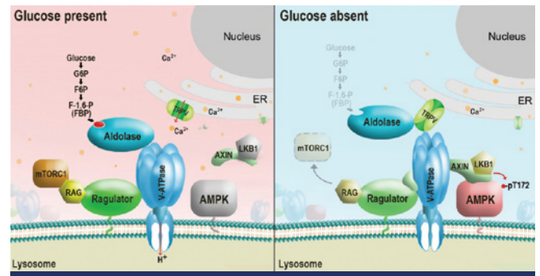
Advancing therapeutic discoveries

Developing therapeutics in response to the national strategy of boosting original drug discovery has been the aim of Deng's team. They are engaged in chemical biology research, focusing on identifying untargeted kinases and validating their pharmacological effects.

Besides developing the MST1/2 inhibitor, Deng's team is also recognized for their studies to understand and target cancers driven by mutations of the RAS family of genes.

RAS proteins act as molecular switches, regulating signalling pathways and other cellular interactions, and when mutated, can cause cancer, including melanoma.

With collaborators, Deng's team has identified a protein kinase, STK19, which regulates NRAS function, and characterized the mechanism by which it works. Based on this discovery, they have designed an STK19 inhibitor that prevents NRAS activation and the development of NRAS-driven melanoma. This finding provides a promising strategy for treating melanoma, as well as other RAS-driven cancers. Research by Deng's team has led to 12 patent applications, and five technological licensing agreements, opening application possibilities for kinase-targeted drugs in cancer treatment and regeneration medicine.



Shengcai Lin's AMPK studies highlight the effect of glucose starvation.

Breakthroughs in targeted therapy have also been made by a team led by XMU professor, Qiao Wu, who has been studying Nur77 (also called TR3), a member of the nuclear receptor superfamily that modulates a variety of physiological functions. Nur77 dysfunction is found to be associated with a range of diseases, including diabetes, cardiovascular diseases, inflammation and cancer.

Wu's team has revealed different signalling pathways and mechanisms by which TR3/Nur77 induces cell death and exerts its anti-inflammation, anti-diabetes and anti-tumour functions. Based on this knowledge, Wu proposed TR3/Nur77 as a drug target, and explored its various functions. They identified lead compounds that can reduce inflammation, blood glucose, and inhibit tumour progression through targeting and modifying TR3/Nur77's functions. Their results have led to journal publications, provincial awards, and invention patents.

Wu's XMU colleague, Xiaokun Zhang, dean of School of Pharmaceutical Sciences (SPS), studies a combined therapy of Nur77 and celastrol, a natural chemical extract from the root of an ivy-like vine.

His team discovered that celastrol specifically targets the immune function of Nur77, and controls inflammation.

Another SPS professor, Ziyan (Chimeng) Tzeng, leads a translational medicine research team that explores using CAR-T technology to treat T-cell malignancies and adenocarcinoma. They identified the target antigens for developing CAR-T cells, demonstrating a viable approach for treating T-cell leukaemia and GBM.

Focusing on Alzheimer's disease (AD), XMU neuroscientists have identified new protein targets and revealed biological mechanisms underlying AD. Their studies provide new strategies for drug development, and informed relevant immunotherapy and gene therapy strategies.

Besides drug discovery, Zuguo Liu, director of the Eye Institute of Xiamen University, has been focusing on corneal tissue engineering technologies. In 2012, he successfully treated a patient by transplanting stromal lamella tissue derived from porcine cornea. This approach brings hope to patients with corneal disease, reducing dependency on donor-derived tissues for replacement therapies.

Liu's colleague, Wei Li, developed tissue engineered corneal epithelium from clinical grade human embryonic stem cells, paving the way for treating severe ocular surface diseases. ■

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