104-10-16

Recent Progress on Medicinal Chemistry-based Anticancer Drug Discoveries from Herbal Medicine-derived Natural Products

李國雄 院士

Abstract

Natural products, especially those derived from herbal medicines, are the best sources for producing new drugs. Plant-derived anticancer natural products have produced numerous novel structure types, which are not likely to be discovered through a single-target or mechanism of action (MOA)-based approach by high throughput screening of general chemical libraries. Dr. K. H. Lee's Natural Products Research Laboratories (NPRL) combines modern medicinal chemistry with cutting-edge life science technologies to investigate Chinese herbal medicines aimed at developing new drugs. This has led to the discovery of several thousand bioactive natural products and their synthetic derivatives/analogs, providing leads for new generation drug design against cancer and other diseases.

In the discovery of new leads, bioactivity-directed isolation and characterization can initially disclose the active compounds from plant sources. Medicinal chemistry plays a very important role for converting these new leads, especially pure single active principles, through modification and synthesis into clinical trial candidates very effectively and efficiently. Examples from the NPRL include GL-331, a synthetic etoposide analog for treating cancer; JC-9, a novel curcumin derivative for treating acne and cancers. Other novel natural products and related compounds from various structural classes, which are currently under preclinical studies will also be presented.

The use of natural products as adjunct therapies to supplement the efficacy and offset the toxicity of Western Medicine is another excellent approach for new drug discovery. One example is the development of PG2 from Astragalus membranaceus to treat cancer-related fatigue, an idea also originated from K. H. Lee.

Overall, there is a bright future for research on medical chemistry-based new anticancer drug discoveries from herbal medicine-based natural products, especially when coupled with recent advances in molecular biology, genomics, and related scientific areas.

104-10-23

Chromatin Organization, Transcription Regulation and Organism Responses

衛嘉玲 教授

Abstract

In multi-cellular organisms, expression regulation is one of the central mechanisms modeling lineage differentiation and cell-fate determination. Much of our current knowledge on how transcription modulating lineage specification was built through the extensive surveys of TF binding sites, epigenetic modifications and gene expressions on the linear genome structure. However, increasing studies demonstrated the communication between regulatory elements is not linear but rather congregating within the large discrete foci termed “transcription factories” in three-dimensional nuclear space. In this talk, I will discuss the approaches used to construct spatial genomic organization and examine the influence of chromatin structure on lineage specific transcription. The current knowledge of chromatin conformation sets the stage for the full-scale dissection of spatial and temporal genome structures and their roles in orchestrating development.

104-10-30

Breast Cancer Susceptibility: from genetic mutation to microenvironment adaptation

李文華 校長

A major breakthrough in breast cancer research came with the substantiation that many of these hereditary cases could be linked to germline mutations in either of two BReast CAncer susceptibility genes, *BRCA1* and *BRCA2*. Mutations in *BRCA1* are believed to account for 50% of hereditary breast cases. Germline inactivation of a single copy of *BRCA1* or *BRCA2* may predispose an affected individual to cancer. I would like to reveal the insight into the process of cancer formation from genetic mutations to adaptation of microenvironment.

Using BRCA-1 as an example, it plays key roles in maintaining genome stability and promoting epithelial cell differentiation. BRCA1 exerts transcriptional repression through interaction with CtIP in the C-terminal BRCT domain and ZBRK1 in the central domain. Impairment of this complex de-represses ANG1 and HMGA2, which stabilizes endothelial cells forming capillary-like network structure and promotes tumorigenesis, respectively. Subsequently, studies have shown that BRCA1 down regulates estrogen and progesterone receptors, which play important roles in breast cancer. However, treatment of Brca1/p53-deficient mice with the progesterone antagonist mifepristone (RU 486) prevented mammary tumorigenesis. These results support the notion that genetic mutations are not sufficient to change epithelial cells to become fully developed cancer.

Genomic instability is the driving force for cancer cells to adapt its microenvironment. Recently, we identified an amplified signal of interleukin-17 B receptor (IL-17RB)/IL-17B as a novel effector critical for breast cancer progression. On the other hand, differentiating epithelial cells secreted interleukin 17E (IL25), which triggered apoptosis through differential expression of its receptor, IL17RB, to activate caspase-mediated cell death. These results suggest that cancer cells select to amplify IL-17RB signals to adapt the environmental changes. Thus, targeting IL17RB of a subset of breast cancer will be an immediate aim to pursue.

Another example to illustrate the impact of microenvironment on cancer cells is from cancer-associated fibroblasts (CAFs). Normally, breast cancer cells alter the nature of its surrounding CAF to secrete many factors including HGF and ADAMTS1 to support its own progression. On the other hand, we also found that fibroblasts secrete SLIT2, which binds to its receptor, Robo1, on cancer cell surface that inhibits its progression through b-catenin pathway. The presence of the Robo1 receptor on cancer cell surface becomes the determinant for responding to surrounding fibroblasts. These results highlight an intricacy between genetic mutations of cancer cells and its adaptation to microenvironment during cancer initiation and progression. Elucidating these intricacies will be the goal of next decade.