Progress in the Discovery of Natural Anti-cancer Agents that Retard Cancer Cell’s Tolerance to Nutrition Starvation

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ABSTRACT:

Human pancreatic cancer cells have remarkable tolerance to survive in conditions of extreme nutrient deprivation. Therefore the search for agents that retard the cancer cells tolerance to nutrition starvation is the novel approach in anti-cancer drug discovery. During past several years, a number of natural anti-cancer agents having activity to diminish this tolerance to nutrition starvation (anti-austerity agents) have been discovered. This presentation will highlight the overview of research in this field to date and the future perspectives.

KEYWORDS: anti-austerity strategy, cancer, nutrition starvation, natural medicine, drug discovery

Cancer is the leading cause of death worldwide. An estimated 7.6 million people died of cancer in 2007 worldwide and it is projected to increase to 11.5 million deaths by 2030. Among the different forms of cancers, pancreatic cancer is known to be the most aggressive disease with the lowest 5-year survival rate. Almost all patients with pancreatic cancer rapidly develop metastases and die within a short period after the diagnosis. The well-known conventional chemotherapeutic agents such as taxol, doxorubicin, cisplatin and camptothecin are virtually ineffective against this cancer. Currently, surgery is the only treatment modality that offers any prospect of potential cure. Therefore, the discovery of effective chemotherapeutic agents is urgently needed.

Human pancreatic tumors are hypovascular and are constantly exposed to stressful microenvironments, including glucose deprivation, hypoxia, and other forms of nutrient starvation. However, cancer cells derived from human pancreatic tumor such as PANC-1, AsPC-1, BxPC-1, KP-3 show the remarkable tolerance against such severe growth conditions and can survive for prolonged periods of time even in the complete absence of nutrition. Thus, development of drugs countering this resistance to nutrition starvation is considered as a novel strategy in anticancer drug discovery. Working on this hypothesis, we developed a novel screening strategy termed as “anti-austerity” strategy and began screening of medicinal plants used in Japanese Kampo Medicine, Ayurvedic medicine and medicinal plants used in different ethnic cultures.

Beginning from the year 2005, we have made rapid progress in the discovery of a number of novel anti-austerity agents from natural medicines. Arctigenin, a butyrolactone lignan was the first anti-austerity agent identified from the Japanese Kampo medicinal plants that displayed potent preferential cytotoxicity and selectively kills 100% PANC-1 cancer cells growing under low nutrient condition at the concentration of 1 μM. Furthermore, arctigenin strongly suppressed in vivo xenograph
PANC-1 tumor growth in nude mice upon subcutaneous injection. The mean time tumor doubling was found to be increased to 49 days compared to the 23 days in control group. A number of subsequent studies on the further nine different pancreatic tumor xenograft showed a strong inhibition of tumor growth in all the tested models, and significantly increased the lifespan of arctigenin treated group compared to the control group. Nearly five years after its discovery as potent anti-austerity agent, it is now under phase II clinical trial at the National Cancer Center Hospital.

Angelmarin, a novel coumarin was isolated from another Kampo medicinal plant *Angelica pubescens* was the most potent compound identified to date with PC100 of 0.03 μM. The total synthesis of this unique anti-austerity agent has been reported by two independent groups together with other angelmarin derivatives and studied their structure activity relationship. An evergreen tree found in Myanmar, *Kayeae assamica* has yielded 18 coumarins, five of them showed tantalizing preferential cytotoxicity against PANC-1 cells at PC100 1 μM. A number of flavanon and flavans with varied anti-austerity activity were isolated from *Bosenbergia pandurata*, *Soymida febrifuga*, pine resin and propolis from different geographical locations. Most recently, we have discovered chrysoplenetin from the seeds of *Vitex negundo* as potent cytotoxic agent, that not only displayed preferential cytotoxicity against PANC-1 cells, but also found to be active against a panel of 39 human cancer cell lines (JFCR-39).

In this presentation, we discuss a brief overview of the progress in discovery of anti-austerity agents from natural medicine together with synthetic efforts and the most recent development in this field to date.

References

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