

Targeting Multiple Signaling Pathways, a Potential Explanation to the Therapeutic Actions of Traditional Chinese Medicine in Cancer?

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Editorial

Traditional herbal therapies such as Traditional Chinese Medicine (TCM) are increasingly used in the treatment of diseases including cancer. These medicines are either a single herb based or frequently made of multiple herbs, based on the combinational benefits of the herbal medicine. The formulations are supported by traditional sometimes ancient theories, others based on practical experience. This has frequently made the understanding of how the medicine(s) works (or potential mechanism) a challenge. However, some of the herbal medicine(s) that have demonstrable and reproducible clinical benefits attracted attention to explore mechanism(s) of action, attempt to separate the active ingredient(s) from the herbs. Artemisinin perhaps serves a good example. The compound is extracted and purified from an anti-malaria Chinese herb QingHao in nineteen seventies and found to be a highly effective anti-malaria medicine. It is now used throughout the world since nineteen nineties as one of the first line treatment for malaria [1]. Another example is the discovery of Taxol from Western Yew barks in the nineties, which (including its derivatives) is now one of the popular frontline drugs for cancer treatment.

However, a few other medicines that have clinical benefits yet clear mechanism(s) and/or active ingredient(s) are yet to be identified. A good example is a TCM formula known as Qili QiangXin which was found to be highly effective in treating heart failure [2]. The clinical effective formulae/herbs may prove to be a fertile ground in search for new medicine and new approaches. Another example is a TCM based treatment, known as HuangQiTang which has been reported with beneficial effects for patients with cancer in meta analysis from published work [3]. Searching for alternative methods in treating cancer and mechanisms of those known to work have been long and continued efforts, a recent example being the Get to Know Cancer Network which drew a large group of international experts in searching for options including low toxic naturally occurring remedies in treating cancer (www.gettingtoknowcancer.org) [4].

YangZheng XiaoJi and Cancer Treatment

We have recently come across a TCM formula, known as YangZheng XiaoJi, which is a prescription only medicine (POM) used for patients with malignant conditions. The medicine formula is made of 16 TCM herbs and has been approved in China for use in patients with cancer including liver and lung cancers [5]. It appears to have an implication in other conditions such as gastric dysplasia. Clinically, the medicine has been found to be able to increase the sensitivity of chemotherapy and at the same time reduce the side effects associated with chemotherapy including weight loss and bone marrow suppression. A recent meta analysis of over 2,000 patients has shown that the

medicine has very low side effects [6]. Beyond the clinical efficacy and observed biochemical and immunological changes with the patients, there have however been little reports on how the medicine works, at a cellular, molecular or genetic level. We have recently taken an interest in this medicine and explored how it might work in the cells with an emphasis on signalling transduction.

YangZheng XiaoJi Extract and Angiogenesis in Tumour Models

Given that the medicine was formulated based on the Collateral Disease theory in Chinese medicine, which strongly implicates a pivotal role of endothelial cells in disease, we first tested the medicine on vascular endothelial cells and angiogenesis [7]. It came to our surprise that the medicine has shown a profound effect on angiogenesis both in vitro and in vivo. In vitro, it markedly inhibited the migration and tubule formation of vascular endothelial cells and more interestingly reduced the phosphorylation of FAK (focal adhesion kinase), a kinase central to cell-matrix, cell migration and intracellular signalling. Subsequently, we have also found that the medicine also inhibits the activation of FAK in malignant cells including osteosarcoma [8].

The Broader Effect of the Medicine on Cancer Cells

YangZheng XiaoJi appears to have a direct effect on cancer cells. For example, a series of cancer cell lines from different tumour types have been shown to respond to the medicine. These cells are originated from human lung cancer, gastrointestinal cancer, pancreatic cancer, endocrine related (namely breast and prostate) cancers and as indicated early, from osteosarcoma [8-10]. The profound response of these cancer cells to YangZheng XiaoJi appears to be cell adhesion and cell migration, and to some degree cell growth. The change in cell adhesion is probably not so surprising, given the observed effect of the medicine on focal adhesion kinase (FAK) in endothelial cells. These studies have further demonstrated that pathways including the AKT pathway, the SHH (Sonic Hedgehog), SRC pathways and HGFR-EGFR transactivation [8-11], which are widely involved in cell migration and cell growth, are responded to the medicine. For example, in a lung xenograft tumour model, the levels of SHH and SMO were reduced in response to the treatment with YangZheng XiaoJi [12].

Potential Implications in Peritoneal Metastasis of Cancer Cells

One of the recent experimental findings with YangZheng XiaoJi is its potential in interfering the interaction between tumour cells and

peritoneal mesothelial interactions. The studies have demonstrated that it is able to reduce the peritoneal metastasis from various gastrointestinal and ovarian cancers [13, 14]. This role of YangZheng Xiaoji was thought to be by blocking CD44-Hyaluronan interactions via its effect on the SRC pathway, downstream of CD44 [13, 14].

YangZheng Xiaoji and a Wider Therapeutic Implication

Although the medicine has been so far given to patients in combination with traditional chemotherapy and radiotherapy, one would argue that the impact of the medicine on multiple signalling pathways may open a new front when considering combined therapies with neoadjuvant agents including kinase inhibitors. Indeed, experimental data from *in vivo* models have shown that the medicine is able to have a synergistic effect with SHH inhibitor, cMET inhibitor and FAK inhibitor [8,11,12]. It is plausible to suggest new clinical studies/trials by combining YangZheng Xiaoji and the respective pathway inhibitors.

Thus, YangZheng Xiaoji has been shown to influence a number of signalling pathways in cancer and endothelial cells. This is interesting as targeting multiple signalling pathways in cancer treatment has been widely proposed [15-17] and that combinational therapies using multiple signalling inhibitors have been trialled presently [18-20]. It is thus possible that a herbal medicine or herbal formula such as YangZheng Xiaoji targets multiple pathways in cancer in a clinical scenario and thus delivers clinical benefits. Of course, future work will contest if this is sensible and viable.

This short editorial aims to provide an overview of the trails of development and findings of a traditional formula in cancer treatment. It is also aimed to excite more interest in researching into traditional medicine that has shown clinical promise. Presently and for the particular medicine discussed in this editorial, one would anticipate a tremendous challenge ahead, including identification of active ingredient(s) or the mixture of active ingredient (s), if further reduction to the size of the formulation can be made, extending the delivery route from oral to other routes to allow room for dosage variation, common tasks for most herbal based medicines. Targeting multiple pathways in cancer is coming and that traditional medicine may well have a role to play here.

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