INHIBITIVE EFFECT OF PRODIGIOSIN ON THE PROLIFERATION OF HUMAN MALIGNANT PANCREATIC CANCER CELLS

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Abstract. Pancreatic cancer is not only common, but also extremely difficult to treat, for which it has been called “the challenge of the twenty-first century”. In this study, we find that prodigiosin could effectively inhibit the proliferation of human pancreatic cancer cells H8898 in a dose-and-time-dependent manner, with an IC_{50} of 75\mu mol according to the results of MTT and cell proliferation assays. This inhibitive effect may relate to two factors: mitotic arrest and cell death. Results of clone formation and Flow cytometry analysis (FCAS) suggested that prodigiosin has the capability of restraining mitosis by regulating the cell cycle. Prodigiosin also could induce apoptosis of pancreatic cancer cells at low concentration and results in the fragmentation pattern of DNA. Prodigiosin may effectively enter cells and promote the level of intracellular reactive oxygen species (ROS) in a dose-dependent manner. The generation of ROS may play an important role in the cytotoxic effect. All these results demonstrate that prodigiosin can obviously inhibit the proliferation of pancreatic cancer cells H8898 by arresting the cell cycle and inducing apoptosis. Increased ROS lead this cytotoxic effect.

Introduction

Cancer of the pancreas has become more common in most Western countries over the past three decades. It is the fourth leading cause of cancer-related mortality in the United States, accounting for 30,000 deaths annually.\textsuperscript{1,2} Pancreatic cancer is a deadly disease with a 5-year survival of only 3–5% and the median survival after diagnosis less than 6 months.\textsuperscript{3} Surgical resection cures only a very small minority of patients. With limited therapeutic options available at this time, it is critical to find new drugs to fight this devastating disease.\textsuperscript{4}

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A family of natural red pigments called prodigiosins are synthesized by various bacteria such as *Serratia marcescens*.\(^5\) Cycloprodigiosin, hydrochloride (cPrG · HCl), uncelylprodigiosin (UP), metacycloprodigiosin, desmethoxyprodigiosin and prodigiosin are congeners. Prodigiosin, with a methoxypyrrole ring, has several biological activities such as immunomodulator, antibacterial, antimalarial, and so on.\(^6\)–\(^10\) Recently, many studies\(^11\)–\(^16\) imply that prodigiosin has a massive potential in cancer chemotherapy, which draws great public attention. The studies about its anticancer effect mainly focused on inducing apoptosis. It has been reported that prodigiosin could induce apoptosis in haematopoietic, colorectal and gastric cancer cells.\(^11\),\(^13\),\(^4\)

Reactive oxygen species (ROS) are generated during respiration in mitochondria as well as by distinct enzyme systems. ROS, as important modulators, have been implicated in the regulation of diverse cellular functions including intracellular signaling, transcriptional activation, proliferation, and apoptosis.\(^17\) The change of intracellular ROS levels has a marked influence on the cell. So, it has been regarded as an important target site for drugs' development.

Based on this, in the present study we have selected prodigiosin, produced by bioengineering technology, as a candidate and characterized its inhibitory effect on the proliferation of human malignant pancreatic cancer cells H8898. Furthermore, we examined whether the underlying mechanism of this effect relates to intracellular ROS levels. This study establishes a foundation for future research of a potential drug to fight pancreatic cancer.

**Methods and materials**

**Cell lines and culture conditions**

Human malignant pancreatic cancer cells H8898 were obtained from the Second Military Medical University. They were cultured in RPMI Medium 1640 (GIBCO BRL, Grand Island, NY, USA) containing 10% dialyzed heat-inactivated bovine serum (BS) (GIBCO BRL) at 37°C in a humidified atmosphere of 95% air and 5% CO₂.