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Extended Abstract

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Production of a prodigious drug with anticancer and immunosuppressive properties

Pendharkar Girish, KBC North Maharashtra University, India
E-mail: gireeshsh08@gmail.com

Prodigiosin is a tripyrrolic pigment that exhibited numerous biological activities including antibacterial, immunosuppressive and anticancer properties. Prodigiosin is reported to kill cancer cell lineages by either inducing caspases dependent apoptosis, DNA intercalation, altering cell signaling pathways or inhibiting the action of topoisomerase I/II. It has been showed cytotoxic effects on hepatocellular carcinoma cells, breast cancer cells and neuroblastoma cells. The present study was aimed at production of prodigiosin and exploring its applications. Peptone glycerol medium (PGM) was used to screen out red colony forming bacteria from waste coconut sample. Pigment production medium was used for production of Prodigiosin. Bacterial culture inoculated in sterile production medium and incubated at 28 ± 2°C at 300 rpm. After incubation cell pellets were harvested and lysed by acidified methanol. Prodigiosin production was confirmed by taking absorbance at 535 nm and by HPLC. On the basis of biochemical tests isolated bacteria was Serratia spp. Nutrient broth did not show accumulation of red pigment in bacterial cells but pigment production medium did. In initial experiments, maximum concentration of prodigiosin synthesized by was 2 g L-1 in pigment production medium. It also exhibited antibacterial activirty against E.coli and Bacillus subtilis. Serratia spp. and pigment production medium could be optimized for a cost effective production of this anticancer drug. The Admet properties for in-silico analysis are under process. Bacterial prodiginines are a family of red-pigmented, tripyrrolic compounds that display numerous biological activities, including antibacterial, antifungal, antiprotozoal, antimalarial, immunosuppressive and anticancer properties. Recently, significant progress has been made in understanding the biosynthesis and regulation of bacterial prodiginines. An understanding of the biosynthesis of prodiginines will allow engineering of bacterial strains capable of synthesizing novel prodiginines through rational design and mutasynthesis experiments. Bacterial prodiginines and synthetic derivatives are effective proapoptotic agents with multiple cellular targets, and they are active against numerous cancer cell lines, including multidrug-resistant cells, with little or no toxicity towards normal cell lines. A synthetic derivative, GX15-070 (Obatoclax), developed through structure-activity relationship studies of the pyrrolic ring A of GX15, is in multiple Phase I and II clinical trials in both single and dual-agent studies to treat different types of cancer. Therefore, prodiginines have real therapeutic potential in the clinic. Based on the analysis of more than 270 patents and scientific articles, this state-of-the-art review presents Ganoderma lucidum, a medicinal basidiomycete mushroom with immunomodulatory and anti-cancer effects. Cultivation methods for the commercial production of G. lucidum fruit bodies and mycelia are summarized, with main active compounds of triterpenoids, polysaccharides, and proteins, often found in forms of proteoglycans or glycopeptides. Pharmacological effects with emphasis on anti-cancer and immunomodulatory functions are presented, separately for spores and dry mycelia, and for the groups of triterpenoids, polysaccharides, proteins and glycoproteins. Patents disclosing preparation methods of extracts and purified pharmaceutical isolates are reviewed, and examples of anti-cancer formulations, used as pharmaceuticals or nutraceuticals, are given. The review suggests that according to the present understanding, the anti-cancer activity of G. Amino acid metabolism is a critical regulator of the immune response, and its modulating becomes a promising approach in various forms of immunotherapy. Insufficient concentrations of essential amino acids restrict T-cells activation and proliferation. However, only arginases, that degrade L-arginine, as well as enzymes that hydrolyze L-tryptophan are substantially increased in cancer. Two arginase isoforms, ARG1 and ARG2, have been found to be present in tumors and their increased activity usually correlates with more advanced disease and worse clinical prognosis. Nearly all types of myeloid cells were reported to produce arginases and the increased numbers of various populations of myeloid-derived suppressor cells and macrophages correlate with inferior clinical outcomes of cancer patients. Here, we describe the role of arginases produced by myeloid cells in regulating various populations of immune cells, discuss molecular mechanisms of immunoregulatory processes involving L-arginine metabolism and outline therapeutic approaches to mitigate the negative effects of arginases on antitumor immune response. Development of potent arginase inhibitors, with improved pharmacokinetic properties, may lead to the elaboration of novel therapeutic strategies based on targeting immunoregulatory pathways controlled by L-arginine degradation. The idea that the immune system can be harnessed to destroy tumors has been pursued for over a century. However, for decades the efforts have mainly focused on stimulating the immune system with recombinant cytokines, immune adjuvants, or co-stimulatory agonists that seemed critical for the induction of potent and sustained immune responses. The rationale was that the immune system in cancer patients lacks sufficient power to mount anti-tumor response. It now seems however, that the interference with pathways dampening lymphocyte reactivity appears to be more effective in cancer patients than over-stimulation of effector mechanisms of immune system. The most successful approaches to impair tumor-elicited immunosuppressive mechanisms turned out to be monoclonal antibodies. The spectacular therapeutic effects with unexpected ability to induce long-term tumor control led to clinical approval of checkpoint inhibitors. Despite unprecedented antitumor efficacy, checkpoint inhibitors are effective in a minority of cancer patients, however. Thus, identification of response biomarkers as well as resistance mechanisms has become a priority for cancer researchers. A number of molecular mechanisms involved in the evasion of the anti-tumor immunity have been characterized in recent years.

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