P2-18

Drug discovery from plant-derived natural products as treatment against pancreatic cancer : Search for choline transporter inhibitors

（大学院修士課程 1 年医学総合研究所）
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Pancreatic cancer is one of the most deadly of all types of cancer and is often difficult to detect. The currently reported five-year survival rate for pancreatic cancer is still extremely low. Early detection and improved treatment strategies are needed to improve the prognosis for this deadly disease. Choline is an organic cation that plays a critical role in the structure and function of biological membranes. Intracellular choline accumulation through choline transporters is the rate-limiting step in phospholipid metabolism, and it is a prerequisite for cell proliferation. In this study, we examined the functional characterization of choline transporters in MIA PaCa-2 pancreatic cancer cells. Furthermore, we searched for compounds that inhibit choline uptake as well as cell proliferation in a plant-derived natural organic compound library. Choline uptake is Na^+-independent and mediated by a single transport system. Choline transporter-like protein 1（CTL1）and CTL2 mRNA are highly expressed. We found two hit compounds that inhibit choline uptake and cell viability from 480 plant-derived natural organic compounds. These hit compounds reduced cell survival and enhanced caspase-3/7 activity. Ceramide, which is an apoptosis-inducing molecule, also reduced cell viability and enhanced caspase-3/7 activity. These results suggest that CTL1 are functionally expressed in pancreatic cancer cells and are also involved in abnormal proliferation. Identification of this CTL1-mediated choline transport system provides a potential new target for cancer therapy. Furthermore, hit compounds inhibit CTL1 function, thereby activating the sphingomyelin metabolic system, and it is thought that apoptosis was induced by endogenous ceramide.

P2-19

膵癌個別化治療を目指した HOXB9 による EMT 誘導と血管新生亢進についての検討

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【背景】 膵癌は消化器癌のなかで最も治療成績の悪い癌腫の一つで、切除率も低く、他の癌腫の様に分子標的治療薬の効果も現状では乏しい癌である。我々の現在までの研究成果により、膵癌以外の癌腫で、転写因子 HOXB9 が上皮間質移行（Epitherial-Mesenchymal Transition ; EMT）や血管新生亢進を通じて癌の転移や浸潤に関わる因子であることが示されており、有意な予後因子であることが示唆されている。以上の知見から、膵癌における HOXB9 発現による EMT や血管新生亢進のメカニズムを明らかにし、膵癌の浸潤・転移の詳細な機構の解明を目的とした。また、膵癌に対する新たな分子標的治療薬の選択の可能性を広げ、個別化治療に対するバイオマーカーの臨床応用確立を目指した。
【方法】 2007 年から 2015 年までに根治切除を施行した膵癌症例を対象として、切除検体における HOXB9 増減と臨床病理学的因子や累積生存率・無再発生存率との相関関係を検討した。膵癌細胞株において siHOXB9 を用いてノックダウンし、細胞形態の変化、EMT marker の変化、血管新生因子の変化、Migration assay における細胞遊走能の変化などを検証した。
【結果】 切除検体の HOXB9 の検討では、HOXB9 高発現群で、有意に血管浸潤陽性、リンパ節転移陽性、術後早期再発などが認められ、HOXB9 発現が無再発生存率・累積生存率の有意な予後因子であることが示唆された。HOXB9 高発現は腫瘍の悪性度の高い群であることが示唆された。*in vitro* の検討では、HOXB9 ノックダウンにより EMT marker、TGFb signature、血管新生因子すべてが抑制されて

いたことが確認された。
【結語】 膵癌においてHOXB9はTGFb経路を介して転移・浸潤メカニズムに関与していることが考えられ、膵癌における個別化治療マーカーとなりうる可能性が示唆された。HOXB9の増減を人為的に制御できれば、癌細胞をMesenchymal-Epitherial-Transition（MET）化し治療効果の向上につながる可能性が示唆された。

P2-20

Usefulness of DCF-R therapy for Stage IV esophageal cancer

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【Background】 In our institution, the chemoradiotherapy for Stage IV advanced esophageal cancer（T4, M1）has been performed. However, the prognosis of 5-FU+CDDP + radiation（FP-R therapy）, which was the standard therapy, was extremely poor, and in 2004 a chemotherapy with Docetaxel added to FP therapy（DCF therapy）was started for improving the prognosis. DCF exerts an excellent effect on M1 cases, but sufficient effect was not obtained in T4 cases. So we started the chemoradiotherapy（DCF-R therapy）for local control in 2007, and obtained good results.
【Purpose】 We report Stage IV esophageal cancer cases and examine the best treatment at the present time by retrospectively comparing the results of different regimen.
【Material and Methods】 The targets were 86 cases diagnosed as Stage IV at the time of initial examination in 1998 to 2014 and treated at our institution. The treatments were Low dose FP + radiation（FP-R）in 1998-2003, DCF alone in 2004-2006, and DCF-R in 2007 and later. The irradiation range was including the main lesion, the N1and N2 lymph nodes and the lymph node of 1.5 cm or more in the FP-R group, and it was 3 cm above and below the main lesion and the range from 1.5 to 2.5 cm wide from the main lesion, and lymph nodes of 1.5 cm or more in the DCF-R group. In each case, the irradiation dose was set to 60 Gy in total.
【Results】 Stage IV cases was 39 : 10 : 57 in FP-R : DCF : DCF-R. Invasion into the large blood vessels was 18/39（46%）: 2/10（20%）: 13/57（23%）, invasion into the trachea and bronchi were 15 cases（38%）: 7 cases（70%）: 23 cases（40%）, and invasion into both organs was 6 cases（15%）: 1 case（10%）: 3 cases（0.5%）. Invasion into the large blood vessels was observed in the FP-R group, and invasion into the trachea and bronchi was observed in the DCF-R group. In the primary effect of treatment, CR was 1 case（3%）: 1 case（10%）: 20 cases（35%）, PR was 18 cases（46%）: 7 cases（70%）: 30 cases %）, and NC/PD was 20 cases（51%）: 2 cases（20%）: 7 cases（12%）. One year survival rate was 21% : 10% : 66%, 5 years survival rate was 6.4% : 10% : 23.2%, median survival was 184 days : 191 days : 429 days.
【Discussion】 DCF-R therapy gave good results in the treatment effect and prognosis for Stage IV esophageal cancer with obvious significant difference compared to FP-R therapy and DCF therapy. Although it was slightly reduced in therapeutic effect in M1 cases, it was considered to be the best treatment at the present time.

P2-21

Differentiation of orbital lymphoproliferative diseases by metabolomics

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【Purpose】 Orbital lymphoproliferative diseases, particularly mucosa-associated lymphoid tissue（MALT）lymphoma and IgG4-related ocular disease（IgG4-ROD）, have similar clinical and also histopathological features, and are therefore often difficult to differentiate. Metabolomics is a method of comprehensive analysis of