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専門 Research Area

病理学

Pathology

研究課題

代表的な研究

がん代謝阻害剤とオートファジー阻害薬の併用による悪性腫瘍制御の試み

100 年以上前から、がん細胞は、正常細胞にはない解糖系エネルギー代謝経路を利用することが提唱されてきた(1924 年 Otto Heinrich Warburg)。現在では、がん細胞は好気状況下でもミトコンドリアの酸化的リン酸化よりも，解糖系で ATP を産生しエネルギーを確保することが、広く知られており、この、がん細胞に特異的な代謝性要求を阻害する薬剤開発が、試みられている。
われわれは、淡明細胞肉腫をがん代謝経路阻害剤 CPI-613®（devimistat）に暴露させると、この肉腫細胞は、細胞質内に蓄えていた豊富なグリコーゲンをオートファジーで処理し、増殖のエネルギーを確保しようとすることを明らかにした。続けて、CPI-613 とオートファジー阻害剤であるクロロキンを併用することにより、淡明肉腫細胞は、グリコーゲンを処理できず、ネクローシスに陥ることを見出した。
このCPI-613とクロロキンの併用に関して米国製薬企業Rafael Pharmaceuticals, Inc. （現 Cornerstone Pharmaceuticals, Inc, NJ）と共同して国際特許、米国各国申請を行い、2021 年 9 月より再発・難治性淡明肉腫を対象に Phase I/II の臨床試験が、米国 6 施設で試行中である。
病理組織学的知見に基づき、淡明肉腫に類似した生物学的態度をもつことが知られている悪性腫瘍を選び出し、がん代謝阻害剤とオートファジー阻害剤の併用による治療方法の適応拡大を試みている。

Main Research Projects

Combination of a cancer metabolism inhibitor and an autophagy inhibitor to control malignant tumors

Nearly a century ago, it was proposed that cancer cells adopt a glycolytic pathway that is absent in normal cells for energy metabolism (Otto Heinrich Warburg, 1924). Now, it is widely accepted that cancer cells generate ATP through glycolysis rather than mitochondrial oxidative phosphorylation, even under aerobic conditions, and agents that could abrogate cancer cell prefer metabolic requirements are under development.
We found that clear cell sarcoma, when exposed to CPI-613® (devimistat, an inhibitor of the metabolic pathway in cancer) use autophagic degradation of the abundant glycogen stock in the cytoplasm to secure energy for cell growth. We also found that use of CPI-613 in combination with chloroquine (an autophagy inhibitor) led clear cell sarcoma cells to necrosis by inhibiting their ability to use stocked glycogen.
Together with the US pharmaceutical company Cornerstone Pharmaceuticals, Inc. (formerly Rafael Pharmaceuticals, Inc.), we have applied for international patents on the combination of CPI-613 and chloroquine in several countries. A phase I/II clinical study was launched in September 2021 to investigate the effectiveness of this approach for treatment of relapsed or refractory clear cell sarcoma and is currently underway at six facilities in the US.
Based on histopathological findings, we plan to select malignant tumors having biological behaviors similar to that of clear cell sarcoma with the aim of expanding the indications for treatment using this approach to those tumors.

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外部資金 (過去 5 年)	1. 平成 29～30 年度　科学研究費助成事業(若手研究(B))　課題番号 17K15642「内因性 2 分子間相互作用の腫瘍組織での可視化検討」
特許	国際特許 3 件 ＃1　WIPO|PCT　WO2020/132395AI(国際特許審査新規性あり、産業性ありで　Taiwan、米国、メキシコ各国申請) ＃2 PCT/JP2022/ 13783(国際特許審査新規性あり、産業性ありで EU および米国各国申請) ＃3 C20210538WO＃P01(特許庁国際出願審査中)
略歴	平成 19 年 3 月　佐賀大学医学部医学科卒業 平成 19 年 4 月　岐阜大学医学部附属病院研修医 平成 21 年 4 月　同病理部医員 平成 26 年 4 月　岐阜大学大学院医学系研究科 形態機能病理学 助教 令和 2 年 3 月　同准教授 令和 4 年 1 月　岐阜大学大学院連合創薬医療情報研究科・准教授 令和 5 年 1 月　岐阜大学高等研究院 One Medicine ﾄﾗﾝｽﾚｰｼｮﾅﾙﾘｻｰﾁｾﾝﾀｰ (COMIT)・准教授　現在に至る。