Protein kinase Cα : its potential for cancer-specific gene delivery and regulaiton of cancer drug resistance

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（プロテインキナーゼＣα：がん選択的遺伝子送達およびがんの薬剤耐性の制御への応用）

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論　文　内　容　の　要　旨

Intracellular signal transduction has prominent roles for many cellular processes in living cells, which is generally modulated by a large number of protein kinases and phosphatases regulating diverse functions, such as proliferation and survival. Because of their critical roles in cellular processes, aberrant activities of intracellular signaling are known to be involved in many diseases. The main objective of this thesis is to focus on abnormally activated intracellular signal, protein kinase Cα (PKCα), as an attractive target, intimately implicated in many cancers and abnormal proliferation and differentiation in transformed cell lines.

Here, I investigate the development of specific and stable gene delivery systems responding to abnormally activated PKCα in cancers, presenting two approaches, using of cationic polymer backbone and introducing of hydrophobic interaction. These cellular signal-responsive systems exhibited quite high transgene expression responding to abnormally activated PKCα, and presented the effective cellular uptake and capable of endosomal escape of polyplexes caused by a strong pH buffering capacity of PEI units at around 5-6 in endosome causing the so-called proton sponge effect, consistent with their efficient transgene expression both *in vitro* and *in vivo*. These approaches are able to be served as an alternative application for cancer-specific gene therapy.

Moreover, I focus on PKCα as an attractive modulator for successful cancer chemotherapy, in which hyperactivated in drug-resistance cancer cells, and propose one potential for reversal of drug resistance by regulating this activated PKCα. The effective inhibition of PKCα activity presented increased drug accumulation in drug-resistant MCF-7/ADR cells, providing evidence that PKCα has a prominent role in the regulation of drug efflux. This approach may improve response of therapeutic drug, and consequently contribute to chemotherapeutic efficacy in drug-resistance cancers.