Patient-derived xenograft models for a strategy to develop drugs targeting cancer cells and microenvironment interaction

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Clinical cancer tissue consists of cancer cells and surrounding microenvironment, which includes stromal cells such as fibroblasts and smooth muscle cells, immune/inflammatory cells, extracellular matrices, nerves or vessels. Although it is gathering attention that cancer cells are genetically or epigenetically heterogeneous, microenvironment is also highly heterogeneous from the aspects of not only its composing cells or matrices but also oxygen and nutrient supplies. Heterogeneity of microenvironment can also change time to time even in short periods. Previously we reported that expression of some genes in cancer cells is synergistically enhanced by hypoxia and deprivation of nutrients, especially lipids, and the change impacts on cancer cell survival, motility or invasiveness[1].

Despite significant efforts are payed on development of anticancer therapeutics, most of them are result in fail and only 5% of anticancer drug-candidates are now evaluated for clinical use. Good preclinical cancer models to be used for precise evaluation of the efficacy are eagerly needed for developing anticancer drugs or treatment modalities and also for personalized cancer treatment. Many preclinical human cancer models are available including immortalized cancer cell lines, cancer cell organoids/spheroids, or patient-derived xenograft (PDX) with merits and demerits in each model. PDX may have some advantages to study cancer microenvironment. Although organoids/spheroids can be used for a source of PDX, differences in cancer cells and microenvironment between original PDX and organoids/spheroids-derived PDX are not yet clearly addressed.

Pancreatic ductal carcinomas are known as interstitium-rich tumor and the microenvironment is revealed to play pivotal roles in the initial carcinogenesis, progression or acquisition of treatment resistance. We are attempting to develop anticancer drugs or novel treatment modalities targeting pancreatic cancer—microenvironment interaction by using PDX in immunodeficient mice[2]. When we decipher the interaction between pancreatic cancer cells and their surrounding microenvironment, the PDX consisting of human cancer cells and mice microenvironment is a good material because of its availability to differentially evaluate gene expression between the two by NGS. Komura et al. has reported this technology as the CASTIN system[3]. I would like to preset some our progress in this attempt.

[References]

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