

Model Tumor System – A Tumor’s Conjecture

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ABSTRACT

Tumor models are approximations of a tumor, designed to reiterate specific characteristics of the tumor microenvironment. They help to perceive the tumor growth, proliferation, migration, invasion, matrix remodelling, dormancy, intravasation, extravasation, angiogenesis, drug delivery, and treatment response assessment. They serve as important tools for cancer research.

Tumor models used for assessment can be either in-vivo tumor models or in-vitro tumor models. Various in-vivo tumor models are transplantable solid tumor systems in experimental animals, xenografts of human tumors, and autochthonous and transgenic tumor models. The in-vitro tumor models generally used are transwell-based models, spheroid-based models, hybrid platforms and tumor-microvessel models.

Development of tumor models that are very specific for various cancers is of utmost importance. Much research is required in this field before the use of model tumor systems widely.

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They are needed to assess the effectiveness of various oncological therapies.²

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Transplantable tumor models can be used for various tumors of different histological types that are grown in laboratory animals. In order to produce a large number of virtually identical tumors, propagation by transplantation is done. It is mandatory to maintain pure inbred strains of experimental animals so as to avoid any discrepancy. The tumor is removed from the patient and prepared into a single-cell suspension with the use of an enzyme, trypsin. Thereafter these cells are forced through a fine wire mesh. 10⁴ to 10⁶ cells are inoculated into each experimental animal subcutaneously. Within few days or weeks, palpable tumor appears in the recipient animals that are uniform in size, type, etc.²

There are various techniques to assay the response of solid tumors to treatment. These are tumor growth measurements, tumor cure (TCD50) assay, tumor cell survival determined in vivo by the dilution assay technique, tumor cell survival assay by the lung colony assays, tumor cell survival using in vivo treatment followed by in vitro assay.³⁻⁵

Xenograft is a transplant done from one species to another. It customarily refers to a human tumor growth transplanted in an experimental animal. If the recipient animal has a normal immune system, then the xenograft should not grow. But there are two techniques by which the growth can be achieved. Experimental animal strains that are congenitally immune deficient can be developed like nude mice, nude rats, and SCID mice. The experimental animals can undergo severe immuno-suppression by the use of radiation or drugs or a combination of both. Neither of these hosts completely fail to repudiate the tumor cells.^{2,6} Drawbacks of xenograft technique are the tendency for the tumor to be rejected, resulting in false tumor control, human tumor cells may undergo kinetic changes and cell selection if transplanted into mice, they are not valid for any studies in which the vascular supply plays an important role.^{2,6}

Autochthonous and transgenic tumor models are the use of certain inbred strains of mice that have high incidences of spontaneous tumors that occur due to viral exposure or carcinogen administration. C3H mice can develop spontaneous mammary tumors due to mouse mammary tumor virus (MMTV) and C57BL6 mice are highly susceptible to develop lymphomas when exposed to ionizing radiation. The advantage of autochthonous tumor model is that they are primary tumors with reproducibility in some organs. They are influenced by the host stroma and immune system and are able to metastasize through the hosts vasculature or lymphatic systems.²

Transgenic animals that possess specific mutations in a given oncogene or tumor suppressor gene have been proposed as better models to study the effects of ionizing radiation than autochthonous mice. Transgenic animal models have the advantage that the effect of a single or few genetic alterations on the response of tumors to radiation could be examined in an immune-competent mouse in a reproducible manner.²

Transwell based tumor models are widely used to assess cancer cell migration and invasion. Three commonly used variations of transwell- based assays are migration assays, Invasion assays, and transendothelial migration assays.⁷⁻⁹ Migration, invasion, and transendothelial migration assays can all be used to assess several parameters like the relative invasiveness of various cancer cells, response of immune cells on invasion of cancer cells, relative rates of migration, intravasation, and extravasation of different cell types, isolation of cancer cell types for molecular analysis, testing the influence of knockdown, transfection, and antibody treatment on invasion and migration, assessing drug therapies in reducing invasion or the effect of gene manipulation.^{1,2,7,8,9}

Spheroid-based models are aggregates of cells grown in suspension or embedded in a three dimensional matrix using three dimensional culture methods. They are approximations of avascular tumor nodules or micro-metastases.^{10,11} They are used for drug screening and studies of tumor growth and proliferation, immune interactions, invasion, matrix remodeling and angiogenesis. They recapitulate cell-to-cell and cell-to-matrix interactions between tumor cells and the microenvironment.¹²⁻¹⁵

Hybrid models are the in-vitro tumor models that cannot be classified as spheroid-based or transwell-based. These include embedded ex vivo tumor sections, 3D invasion models, and avascular microfluidic models. These models combine the complexity of the tumor microenvironment while maintaining the relative simplicity of an in-vitro model.¹⁶⁻¹⁸

Tumor micro-vessel models consist of micro-vessels that are constructed by seeding endothelial cells into predefined extra-cellular matrix scaffolds or self-assembled through matrix remodeling after randomly dispersing endothelial cells within an extra-cellular matrix. They are used to assess interaction between tumor cells and the tumor vasculature.¹⁹

Development of tumor models that are very specific for various cancers is of utmost importance. They may help to perceive the individualized tumor growth, proliferation, migration, invasion, matrix remodelling, dormancy, intravasation, extravasation, angiogenesis, drug delivery, and response assessment. Much research is required in this field before the use of model tumor systems widely.

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