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Modular Recombinant Transporters

►Modular Transporters

Modular Transporters

Alexander S. Sobolev
Department of Molecular Genetics of Intracellular Transport, Institute of Gene Biology,
Russian Academy of Sciences, Moscow, Russia

Synonyms

Modular recombinant transporters; Multi-domain transporters

Definition

Modular transporters are engineered ►polypeptides consisting of several interchangeable parts, or ►modules designed for delivery of anti-cancer drugs to the target cancer cell and its specific subcellular compartment.

Modular transporters can also be considered as nanomedical drug vehicles (►nanotechnology), which recognize the cancer cells of choice, and once in those cells, are transported to the most sensitive compartment of the cell (e.g. nucleus).

In order to reach the desired compartment of the cancer cell, the modular transporters are first passively delivered to the surface of the cell in the blood stream. Once within the cell, depending upon the nature of the ►polypeptide modules, they are transported to a particular ►subcellular compartment utilizing the cell's intrinsic transport machinery.

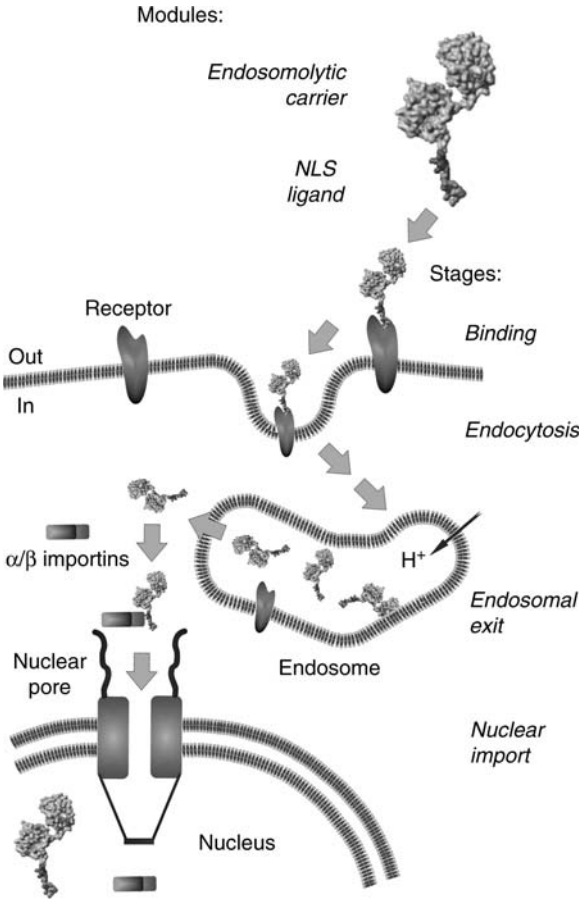
Characteristics

Objectives

To minimize side effects, many anti-tumor agents need to be delivered (►drug delivery) not only to the target cancer cell but also into a specific subcellular compartment, usually into the most sensitive/vulnerable site of the cancer cell. Examples of such anti-tumor agents are: (i) foreign DNA for cancer gene therapy, (ii) ►photosensitizers for ►photodynamic therapy or (iii) ►radionuclides emitting ►alpha-particles for endoradiotherapy (►radioimmunotherapy). All of the above should be delivered into the nuclei where they can perform their specific function. On the other hand, (iv) toxins, most of which are active in the cytosol, require a different modular transport strategy to retain in the cytoplasm.

Principles

This goal can be achieved with the use of modular transporters with preset properties, which would ensure recognition of the desired target cell and subsequent directed transport to the subcellular compartment of choice. The necessity of different modules is determined by the following considerations. First, cell type specificity together with internalization into the target cell can be achieved if the engineered transporter possesses a ►ligand module, which has high binding affinity to the ►receptor overexpressed on the target cancer cell but not on non-cancer cells. This highly specific ►ligand-receptor binding will ensure recognition of the target cell as well as a subsequent receptor-mediated ►endocytosis. The internalized transporter will then be delivered to endocytotic vesicles, or endosomes, localized in the cytoplasm (►endosomal compartments). Second, because the internalized transporter moves along the endocytotic pathway, it is necessary to provide the transporter with an endosomolytic module enabling the transporter's escape from the endosome. Third, a specific subcellular delivery can be achieved if the transporter has a specific localization amino-acid sequence, e.g. a nuclear localization sequence to target the cell nucleus. Finally, the modules as well as the anti-tumor agent should be integrated into one moiety; this goal can be achieved by inclusion of the fourth module, a carrier module. Therefore, modular transporters for nuclear drug delivery should include the following parts: (i) an internalizable ligand module providing for target cell recognition and subsequent receptor-mediated endocytosis; (ii) an endosomolytic module ensuring escape of the transporter from endosomes; (iii) a module containing a nuclear localization sequence (a sequence of amino acids that is recognized by ►importins needed for the active translocation into the nucleus); and (iv) a carrier module for attachment of an anti-tumor agent (Fig. 1).



Modular Transporters. Figure 1 Scheme of a modular transporter, and stages of its transportation within the target cell. NLS, nuclear localization sequence. *Arrows* indicate successive steps of the transporter binding to over-expressed internalizable receptors on the target cancer cell, internalization, endosomal localization within an acidifying milieu, escape from endosomes, binding to importins, and transport through the nuclear pores into the cell nucleus. (From Rosenkranz et al (2003) Recombinant modular transporters for cell-specific nuclear delivery of locally acting drugs enhance photosensitizer activity. FASEB J 17:1121–1123, with permission.)

Features

Fundamental to the success of this strategy is that the modules are functional within the transporter, i.e. they retain their activities within the chimeric molecule. Depending on the type of target cancer cells, the ligand module can be replaced; the module with subcellular localization signal can be replaced or omitted (e.g. omission of the nuclear localizing signal will leave the transporter in the cytoplasm of the target cell).

Several types of modular transporters have been created that can deliver photosensitizers into the nuclei of ►melanoma cells; photosensitizers and radionuclides into the nuclei of glioma and epidermoid carcinoma cells and toxins into the cytoplasm of ►acute myeloid leukemia cells. In all these cases, cell specificity was achieved by inclusion of a specific ligand module into the transporter that bound to a corresponding internalizable receptor overexpressed on the surface of the target cancer cell: melanocortin-1 receptor, epidermal growth factor receptor (►epidermal growth factor receptor inhibitors), (►tyrosine kinase receptors), and interleukin-3 receptor (►cytokine receptor as target for immunotherapy and immunotoxin therapy), respectively. Anti-tumor agents carried by these modular transporters acquired a significantly higher efficacy aside from cell specificity. In cases when they are delivered into the most sensitive sites of the target cancer cells, the agents become 10–3,000 times more effective.

References

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Module

Definition

A standardized, often interchangeable component of a system or construction that is designed for easy assembly or flexible use.

►Modular Transporters

Mohs Micrographic Surgery

Definition

(MMS) is a surgical technique for the removal of certain cutaneous carcinomas that allows precise microscopic marginal control by using horizontal frozen sections. For example, MMS has become the treatment of choice for basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) at high risk for local recurrence.