''बेटी बचाओ, बेटी पढ़ाओ''

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Program : 7^{th} sem.

Course Name : BMLT

Session No. & Name : 2023

Academic Day starts with –

- Greeting with saying **'Namaste'** by joining Hands together following by 2-3 Minutes Happy session, Celebrating birthday of any student of respective class and **National Anthem**.

Lecture Starts with- Review of previous Session- Tumor marker

Topic to be discussed today- Today We will discuss about the on cofoetal antigen and the estimation of method.

University Library Reference- satyanarayan, palmer.

National song' Vande Mataram'

TOPIC : Oncofoetal Antigen

Oncofetal antigens are substances which are produced by tumors and also by fetal tissues but they are produced in much lower concentration by adult tissues. The oncofetal antigens which have been identified are reviewed. The relevance of alpha - 1 - fetoprotein (AFP) and carcinoembryonic antigen (CEA) in neoplastic disease are summarized. Elevated serum concentrations of AFP have been principally associated with primary liver cell cancer (82 percent) and with ovarian and testicular tumors which contain yolk sac tumor cell elements. Quantitation of the serum concentration of CEA can be used as an adjunct for the diagnosis and staging of colon cancer patients and for the post operative follow up of patients for tumor recurrence. The possible role that mouse monoclonal antibodies will play in the characterization of oncofetal antigens is reviewed.

Identifying tumour-associated antigens with therapeutic relevance

There has been considerable effort directed at the development of immuno therapeutic approaches for the treatment of cancer; many of which depend on targeting TAAs. While numerous TAAs have been identified, not all have the appropriate properties to enable safe and effective immune targeting. Such properties include a highly restricted expression profile on normal tissues but broad expression across many different cancer types. Furthermore, cell surface expression is an important property for antibody-targeted therapies while the lack of a tolerised repertoire providing for suitable antibody or cell-mediated adaptive immune responses is critical to vaccine approaches.

5T4 trophoblast glycoprotein (TBPG)

Antigen identification, structure and expression

5T4 Trophoblast glycoprotein was discovered in the context of trying to identify shared cell surface molecules that may function to allow survival of the foetus as a semi-allograft in the mother, or a tumour in its host. The rationale was that such shared expression would reflect common functions relevant to growth, invasion or altered immune surveillance in the host. Murine monoclonal antibodies were raised against purified glycoproteins from trophoblast membrane preparations from term human placenta and initially screened against different cancer cell lines and human peripheral blood mononuclear cells. Further screening using the 5T4 monoclonal antibody (mAb) by immuno histochemistry indicated the antigen was expressed by many different cancers but with a restricted normal tissue distribution

5T4 and tumour-initiating cells

There is increasing evidence for key sub-populations of tumour-initiating cells reflecting normal tissue renewal properties retained and exploited for advantage by developing cancers. Poorly differentiated tumours in NSCLC have been associated with shorter patient survival and shorter time to recurrence following treatment. Using multiple experimental models with clinico-pathologic analysis of patient tumours to delineate a cellular hierarchy in NSCLC, it has been shown that 5T4 is expressed on tumour-initiating cells and associated with worse clinical outcome. Despite heterogeneous expression of 5T4 in NSCLC patient–derived xenografts, treatment with an anti-5T4 antibody–drug conjugate resulted in complete and sustained tumour regression. Thus, the aggressive growth of heterogeneous solid tumours can be blocked by therapeutic agents that target a 5T4 expressing subpopulation of cells near the top of the cellular hierarchy.

5T4-associated functions

5T4 and epithelial mesenchyme transition (EMT)

Over expression of 5T4 in normal murine epithelial cells is associated with E-cadherin down-regulation [14] which is a key component of EMT; this occurs during embryonic development and is important for the metastatic spread of epithelial tumours . 5T4 was shown to be a marker of the early differentiation of mouse and human embryonic stem (ES) cell, and this process involves an E- to N-cadherin switch, upregulation of E-cadherin repressor molecules (Snail and Slug proteins), increased matrix metalloproteinase (MMP-2 and MMP-9) activity and motility, all classic EMT features

5T4 modulation of chemokine signalling

5T4 molecules have been shown to be involved in the functional expression of CXCR4 at the cell surface in some embryonic and tumour cells [36, 37]. Both CXCL12 and CXCR4 expression have been associated with tumourigenesis in many cancers, and it is believed that CXCR4 expression facilitates the spread to tissues that highly express CXCL12 including lung, liver, lymph nodes and bone marrow [38, 39]. 5T4 is expressed by putative leukaemia initiating cells in BCP-ALL, and these cells show the associated property of CXCL12/CXCR4 chemotaxis [30]. 5T4-positive leukaemia-initiating cells are likely attracted by CXCL12 produced by extramedullary sites where there is decreased therapeutic bioavailability leading to disease relapse following treatment.

5T4 modulation of Wnt signalling

Wnt protein intracellular signalling is a central component of many aspects of cellular regulation critical to normal development, homoeostasis and regeneration, while misregulation can lead to disease, including cancer [41]. There are two pathways, the most characterised being the canonical Wnt/β-catenin pathway while non-canonical Wnt signalling through a cell autonomous planar cell polarity (PCP) type pathway can drive the modulation of actin and microtubular skeletons facilitating cell movement in development of cancer.

5T4 has been shown to interfere with Wnt/β-catenin signalling and concomitantly activate non-canonical Wnt pathways.

Exploiting 5T4 expression for cancer therapy

The selective pattern of 5T4 tumour expression, association with a tumour-initiating phenotype plus a mechanistic involvement with cancer spread have underwritten the development of several different immunotherapeutic strategies (see Fig. 1). The approaches which have reached clinical development include a vaccine, a tumour-targeted superantigen and an antibody drug conjugate.

5T4 vaccine development

Preclinical studies

Prior to the clinical development of a vaccine approach targeting 5T4, it is important to show therapeutic activity in animal tumour models and the presence of a T cell repertoire in humans; results from such studies are described below. The availability of a 5T4 KO mouse provided an opportunity to analyse the mechanisms by which endogenous expression of 5T4 influences autologous T cell immunity and tolerance. 5T4 is expressed in the murine thymus and could potentially influence the repertoire and/or induction of specific regulatory T cells (Tregs) impacting either natural or vaccine-induced immunity. Vaccination of 5T4KO mice with a recombinant adenovirus vector expressing murine 5T4 produced strong responses to CD8 and CD4 m5T4 T cell epitopes, while in wild-type (WT) mice the responses were either significantly reduced (only low avidity CD8) or absent (CD4).