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Transfection with Sodium Iodine Symporter Gene (NIS) and Future Applications with Radioiodine Treatment

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Abstract

Human sodium iodine symporter gene (NIS) is the responsible factor for the effectiveness of radioiodine treatment in differentiated thyroid carcinoma. Previous studies in the literature have shown that loss of the NIS gene expression is the reason of ineffective treatment and dedifferentiation of the thyroid cancer. Definitely radioiodine treatment is the most effective cancer treatment method in the world. Probable applications of this treatment to the other types of tumors (like breast cancer, prostate cancer ect.) was the expected and wanted outcome of previous related studies which would be preferable to any kind of other treatments like chemo or radiation therapy. This has been achieved by transfection of cell lines with NIS gene by viruses. Additionally there have been these kinds of studies in the literature however none of these studies consist a stimulating factor like thyrotropin (TSH) for thyroid carcinoma. In radioiodine treatment the cornerstone of the treatment modality is the increased TSH levels in the plasma which can be achieved by withdrawal of thyroid hormone or recombinant TSH preparations. The TSH rich environment is the requirement of radioiodine treatment protocol. The future direction in radioiodine treatment would be the addition of a stimulating factor in the treatment environment. This stimulating factor might be TSH or other stimulants for various different cancer types like prostate specific antigen (PSA).

Keywords: Sodium iodine symporter; Radioiodine; Radiovirotherapy

Introduction

The NIS expression of the tumor tissue is the key point of how the tumor will respond to radioiodine treatment [1]. NIS is responsible of oxygen-dependent transport of Na and I and it is located in the basolateral membranes of the thyroid cells [2]. Unfortunately there are other tissues in the body that has NIS receptors which are salivary glands, breast tissue; which will be evaluated later in this review. The major determinant of this NIS mediated uptake is thyrotropin (TSH) which regulates both NIS and thyroid peroxidase (TPO) and thyroglobulin (Tg) expression [3]. TSH has effect on the NIS mediated iodine accumulation in thyroid cells and would probably have same effects in target tumor cells. Thus in our opinion TSH might have positive effect on the iodine accumulation but this theory has to be verified with in vitro or experimental studies firstly before clinical applications. TSH administration may be performed by recombinant TSH preparations which are in routine usage. TSH is also the key point of radioiodine treatment. In radioiodine treatment protocol elevation of TSH to at least 25-30 levels is considered necessary [4].

Thus in radioiodine treatment for other type of tumors by NIS transfection (radiovirotherapy) should also include TSH rich environment in our opinion. Additionally previous studies support this opinion which has demonstrated that TSH significantly stimulates increase in the NIS m-RNA and protein levels [5]. How to overcome TSH's effects in the other cells like thyrocytes is a meter of debate. There are various protocols in the literature to block the effect of TSH in the normal thyroid tissue, and other cell types expressing NIS which will be mentioned in the following. Experience in the field of radioiodine treatment has shown that it is not possible to treat thyroid carcinomas that has lost their differentiation thus dedifferentiation is the most important problem for thyroid carcinoma treatment.

First applications: Breast cancer

The normal breast tissue concentrates iodine as we experience in radioiodine treatment in routine applications. Additionally this unwanted concentration becomes a problem in especially lactating breast. The dose considerations during iodine treatment include stopping the lactation previously and after the treatment. Although focal iodine accumulation in breast is considered warning for malign breast tumors there are some exceptional cases that might have focal iodine accumulation in their breasts without malignancy in routine practice (Figure 1). This unwanted effect has led to some investigations whether iodine accumulates in malign breast cancer tissue besides normal and lactating breast in the past. The treatment trials in breast cancer patients concluded that there might be potential for the role of radioiodine treatment in the future [6-8].

Joseph et al. [6] have demonstrated that the iodine concentration is higher in the tumor tissue compared to the normal breast tissue [6]. Additionally other investigators have shown the iodine accumulation in the breast tumors which is presumed to be mediated by NIS expression and not suppressed by perchlorate although normal breast tissue and thyroid is [9,10]. Joseph et al. [6] also investigated the effect of stable iodine in three patients and observed no change in pertechnetate uptake in breast tumor tissue [6].

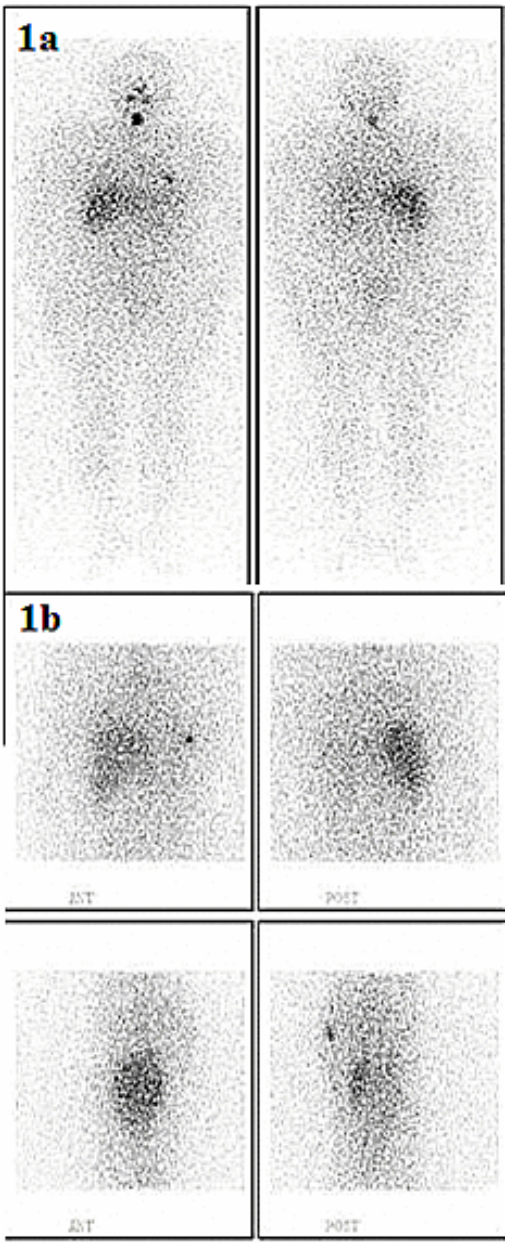

Figure 1: 33 years old, female; her pathological result was papillary thyroid carcinoma follicular variant (3x5 cm). She received 100 mCi radioiodine treatment posttreatment scan revealed residual uptake in neck and increased focal activity accumulation in her left breast (Whole body, spot anteroposterior and spot lateral images from chest). Ultrasonographic imaging from breast revealed nothing and her diagnostic scan was normal in one year follow up.

Although they have concluded in their study that radioiodine uptake of tumor tissue is higher than normal breast tissue and pertechnetate uptake resembles the NIS expression the effect and dynamics of high dose radioiodine has to be demonstrated by future studies.

Strategies in viral radiotherapy

Synergistic effects of viral treatment and NIS has been demonstrated and additionally viral treatment and external beam treatment has been performed together with great success. A triple strategy including additional radioiodine therapy has not been investigated and the necessity is questionable. In our opinion increasing NIS expression with suitable environment for radioiodine treatment would provide the most efficient treatment method. The decision of the mediators like TSH or other tissue specific stimulant may be bring the success. In the future there might be no tumors which require other treatment options than radiovirotherapy.

However dose considerations have to be re-evaluated regarding high doses required for radioiodine part of the treatment. The experimental studies have pointed that approximately 500 mCi for a single treatment may be required. These doses are much higher than our routine applications (200 mCi for metastatic tumors). Additional environmental stimulations may increase these doses thus safety of the iodine treatment might be preserved.

Grünwald et al. [11] have investigated the NIS mediated radiovirotherapy and have demonstrated by I-123 gama camera imaging the synergistic effect of radioiodine and viral therapy [11]. Recent studies have demonstrated generally that additional external beam therapy or radioiodine therapy instead of viral therapy alone may benefit for tumor eradication [12]. Recently Trujillo et al. [13] have decided the suitable radioiodine dose required to treat prostate cancer in the mice and have found that 1 mCi is the optimal therapeutic dose; 0.5 mCi is not enough to promote a response and 2 mCi has no additional effect [13]. They have calculated that these doses contribute to 248 to 496 mCi in human. They have finally achieved slow growing tumor and prolonged life.

Dedifferentiation of thyroid cancer

Dedifferentiation is the most important problem in thyroid cancer treatment. It has been accepted that an anatomical lesion that do not have iodine uptake contributes to dedifferentiated tumor (Figure 2).

However there are some arguments whether to accept iodine negativity in diagnostic scan or post treatment scan or increase in fluorodeoxyglucose (FDG) uptake as dedifferentiation. Usually patients with dedifferentiation present with elevating Tg levels with positive FDG accumulation and negative iodine uptake (Figure 3). However generally iodine negativity is considered as dedifferentiation and which means the prognosis is not good especially with positive FDG accumulation.

There are further medical treatment options (tyrosine kinase inhibitors) for this kind of patients however the long term follow up results of these treatments are not achieved completely since these are new treatments. There have been some particular cases treated with sunitinib (Figure 4).

67 years old female patient; has diagnosis of papillary thyroid carcinoma (1.4 cm, capsular invasion, 2 metastatic lymph nodes) and received 150 mCi radioiodine treatment. She received 150 mCi one year later because of pretrakeal lymph node metastasis and three years later additional 200 mCi for progression and pulmonary metastasis. Dedifferentiation was observed thus she received sunitinib treatment and response was achieved three months later. However in the follow up progression was observed during the sunitinib treatment.

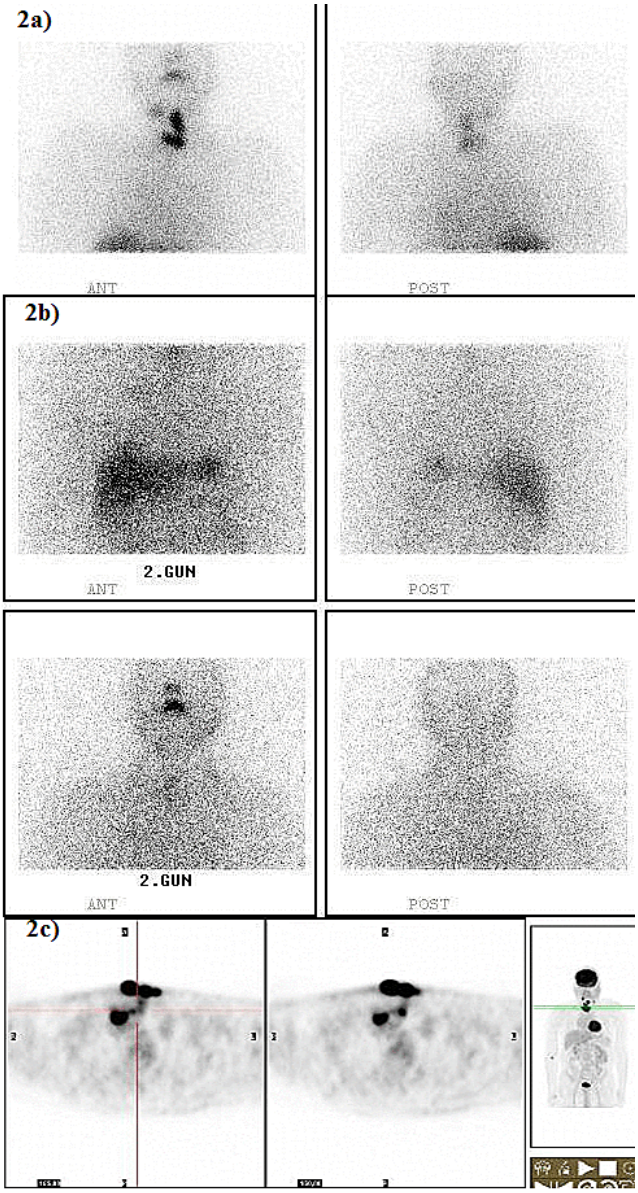

Figure 2: 61 years old, male patient; underwent total thyroidectomy operation three years ago. His pathological result was papillary thyroid carcinoma (7 cm) with capsular invasion and one metastatic lymph node. He received 100 mCi treatment. (Figure 2a: posttreatment anteroposterior images including neck and thorax regions). Three years later he received second 100 mCi treatment because of elevating thyroglobulin posttreatment scan revealed low uptake in residual tissue and pulmonary metastasis with high thyroglobuline levels (94) (Figure 2b: posttreatment images in anteroposterior projection including neck and torax and abdomen) however PET/CT scan showed additional servical and mediastinal subcutaneous metastatic lymph nodes (Figure 2c: PET/CT transaxial, multiple intensity projection images).

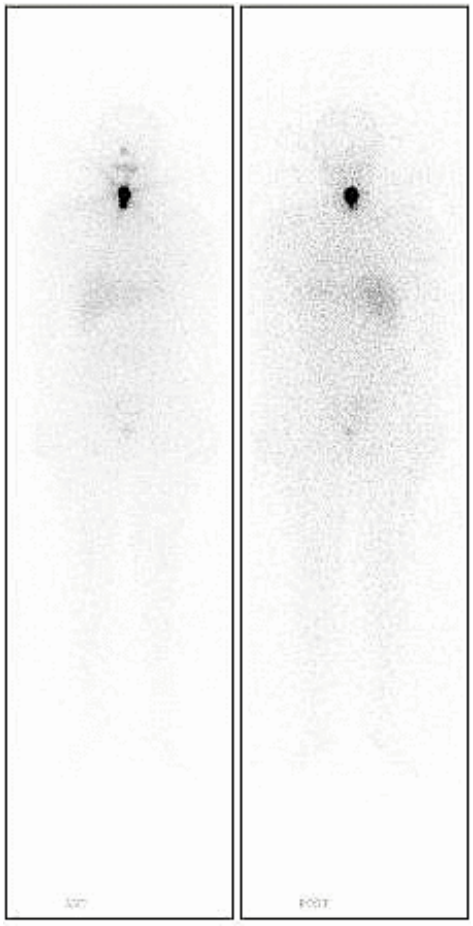

Figure 3: 40 years old female patient; she had multifocal papillary thyroid carcinoma (0x1 cm and 1x5 cm) with capsular and lymphovascular invasion who was operated three years ago. She received 100 mCi in first diagnosis (Figure 3a: posttreatment whole body scan in anteroposterior projection) and two years later a second 100 mCi treatment for elevating Tg levels.

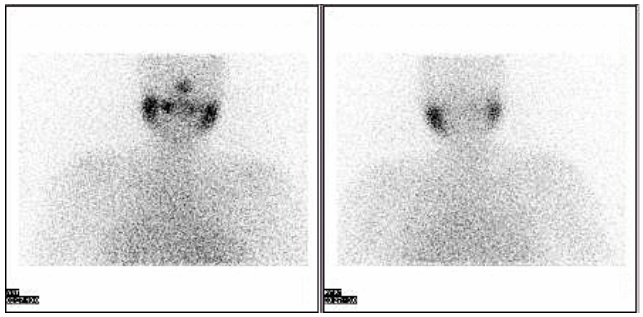

Figure 3b: posttreatment anteroposterior spot images from neck and thorax. Her Tg levels continued to increase despite treatment to 59 ng/mL and PET/CT images revealed two lymph node metastasis in neck.

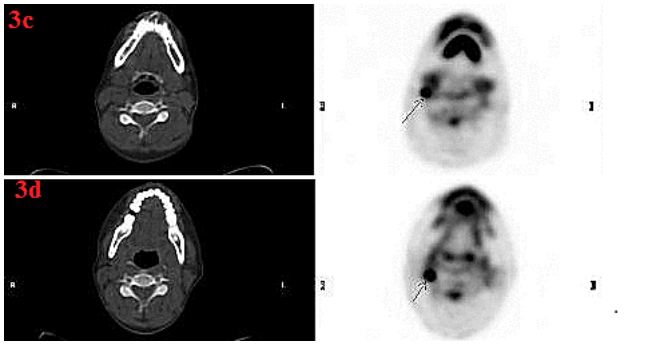

Figure 3c and 3d: transaxial CT and PET images pointing hypermetabolik lymph nodes with arrows.

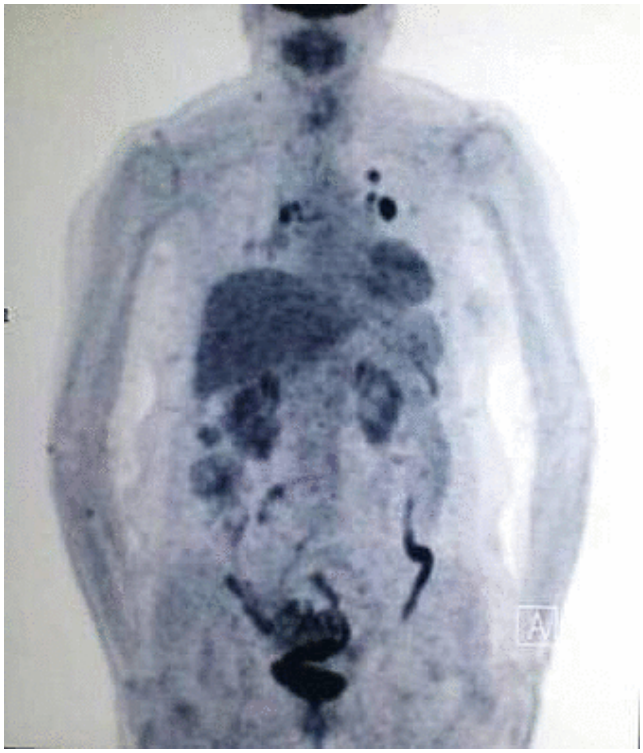

Figure 4a: Follow up PET/CT images in transaxial and multiple intensity projection respectively; progression was observed in 5 month period) and treatment was stopped.

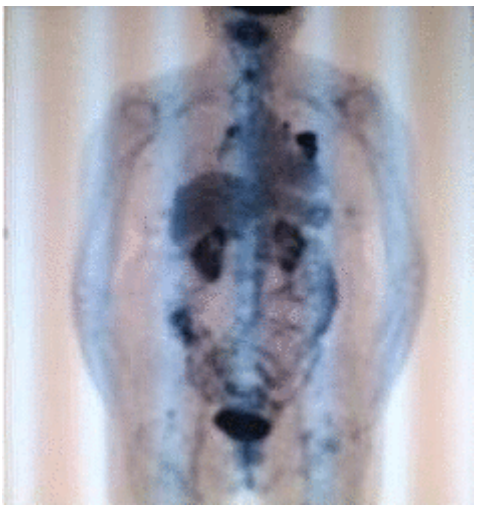

Figure 4b: Follow up PET/CT images in transaxial and multiple intensity projection respectively; progression was observed in 5 month period) and treatment was stopped.

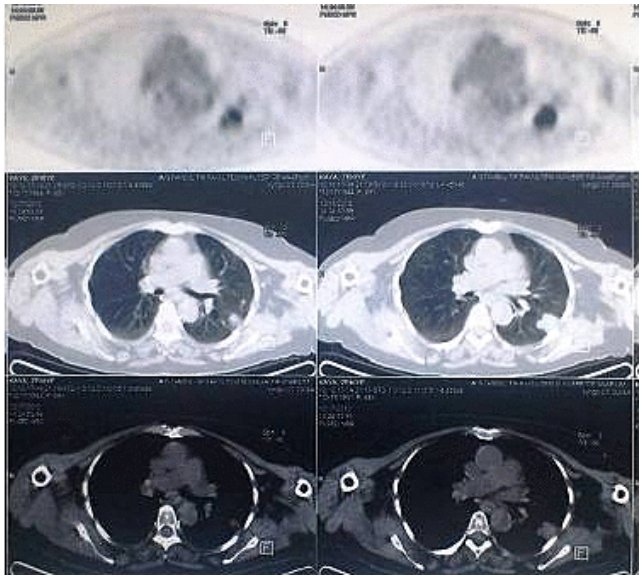

Figure 4c: Follow up PET/CT images in transaxial and multiple intensity projection respectively; progression was observed in 5 month period) and treatment was stopped.

The reasons of dedifferentiation are not clearly documented. Previous diagnostic scans with iodine have been accused and always it has been accepted that the first treatment dose should be as high as it can. In a previous study it has been discovered that pretreatment with I-131 treatment enhances dedifferentiation in thyroid carcinoma which was the explanation of the problem called 'stunning' which was known for years [14]. Additionally they have found that the radioiodine uptake is not solely bound to the NIS expression but other factors are present. They have observed that besides NIS expression there is down regulation of TSH receptor, TPO and Tg associated proteins [15].

According to some of the previous studies NIS transfection did not provide the expected outcome in the success of the radioiodine treatment dedifferentiated tumors [15]. Huang et al. [16] have conducted a study including both NIS and TPO transfection before radioiodine treatment in non-small cell lung cancer (NSCLC) cell line and have achieved success they attributed this success to the absence of Tg expression and presence of TPO expresison in lung cancer cells [16]. However they have notified that this success can only be achieved in lung cancer cells not other cell types [16]. Human TPO transfer has been performed in anaplastic thyroid carcinoma also [17].

Additionally (thyrotropin receptor) TSHR gene transfection has been performed in dedifferentiated follicular cell cancer cell line [18]. TSHR gene transfection has revealed approximately 3 times higher iodine concentration and increase in expression of NIS, TPO and Tg mRNA's.

Other methods in dedifferentiation

Since application of radioiodine treatment to other tumors than thyroid cancer was probably beyond our dreams before. However these exciting developments are hampered by lower efficiency of the method than expected. Thus additional interventions are necessary for radiovirotherapy.

Improving methods for radioiodine treatment have been performed previously like lithium or retinoic acid administration with the treatment however none of these interventions became standard for the procedure. The only standards are requirement of a previous complete surgical removal of thyroid gland and elevation of TSH levels. Low iodine diet previous to the treatment is also a suggested prerequisite however it is not routinely controlled by urine iodine measurements. Which of these interventions are also required for radiovirotherapy is not clear. Additionally other methods' (retinoic acid or other drug administration) did not become the routine practice. However viral treatments may be considered as the most effective additive method for radioiodine treatment. Another important problem about radiovirotherapy is the normal thyroid tissue and how to block thyroidal uptake. Normal thyroid tissue is the natural target of the iodine and in order to prevent thyroidal uptake there have been some applications in previous studies; total thyroidectomy or stable iodine administration in experimental studies.

Radioiodine treatment in differentiated thyroid carcinoma is an established treatment by previous large series [19]. It has been known that non thyroidal tissues also express NIS however only small part of these NIS expressing tumors do show iodine uptake [20]. The NIS expression in other tissues than thyroid tissue like salivary glands, gastric mucosa and mammary gland are lower than thyroid tissue [21]. Additionally it has been observed that malign breast tissue as well as benign breast tissue may retain iodine and thus the first applications cover breast cancer with NIS transfection [9]. In order to accelerate iodine concentration in NIS expressing artificial tumors total thyroidectomy or radioiodine ablation have been performed in tumor bearing animals previously [22]. Additionally retinoic acid or other drugs have been employed in order to facilitate the effect of NIS mediated radioiodine treatment [23,24]. Other therapeutic agents like Re-118 and At-211 have been used with NIS gene therapy previously [25]. In order to improve the therapeutic effect of radioiodine stable iodine administration, thyroid hormone replacement and antithyroid drugs have been employed in previous studies [26]. In medullary thyroid cancer iodine uptake have been restored by recombinant human NIS linked with calcitonin promoter [27].

Viruses: Measles virus

Encouraging studies with measles virus in multiple myeloma treatment has been achieved in human subjects. These results contribute to some hope for prolonged survival in multiple myeloma patients which is considered as one of the most mortal malignancy. Additionally measles virus mediated treatment adjunct to external beam radiotherapy has achieved success. Integration of viral treatment to routine external beam radiotherapy may benefit in the future.

Dingli et al. [28] have performed multiple myeloma treatment by radiovirotherapy by measles virus in mice [28]. Measles virus is a lymphotrophic virus thus was preferred vector for multiple myeloma treatment in that trial and the researchers achieved complete remission with a single dose of I-131 treatment [29]. The researchers preferred measles virus expressing NIS because their previous experiences with the Edmonston vaccine strain of measles virus did not perform satisfactory patency [30]. Their experience with myeloma model has been very promising and probably there will be treatment options for myeloma patients in the future. However the authors have pointed that additional stem cell transplantation might be necessary additional to radiovirotherapy [28]. The researchers are working on the methods that might increase the specificity of the treatment method like targeted receptors like CD38 [28].

Measles virus also has the potential to perform synergistic effect with external beam radiation [29] and previous studies have been performed with MV-NIS [30-32]. In a previous study it has been observed that combination of I-131 with external beam radiation and MV-NIS treatment might increase the efficiency and survival rates of the treatment [29].

Viruses: Adenoviral advances

The most preferred vectors are adenoviruses in radiovirotherapy. There is particular effort in order to improve the effect of adenoviral treatments. Modified vectors and dendrimer coating are new methods performed in order to facilitate the effect of adenoviral mediated treatments.

Oneal et al. [33] have generated two new modified vectors and named 'Ad5/3PB-ADP-h NIS and Ad5/3PB-h NIS [33]. They have performed SPEC/CT imaging additionally and have achieved significantly different results; increased specificity and therapeutic efficiency in a prostate cancer model [33]. Successful treatment has also been achieved by androgen-inducible expression of prostate cancer cell line by prostate specific antigen promoter with NIS gene [34]. A previous study has suggested that despite lack of organification in prostate cell cancer line prolonged retention time and therapeutic efficacy may be achieved [35].

Grünwald et al. have recently generated Ad5-CMV/NIS and Ad5-E1/AFP-E3/NIS and investigated their effect by I-123 scintigraphy [36]. Since the adenoviruses have radiosensitizing potential and ionizing radiation has the potential to increase transduction and replication of the adenoviruses the authors have preferred the adenoviral vectors [33,36-38]. They have performed the 'dendrimer coating' and have overcome the therapeutic defect as a result of lack of organification in non thyroidal tissues and have achieved less liver toxicity as in previous studies [39,40]. Same researchers have investigated the epidermal growth factor receptor targeted adenovirus dendrimer coating as an improving factor for NIS therapy in another study which was considered a promising method in previous studies [41-44].

Future directions

This treatment option has many years history [45]. Various viral vectors have been performed since the first introduction [46]. Adenoviruses and herpes viruses are the most common types and high viral titers have been reached which allows treatment [12]. These developments lead to more efficient treatment options for radiovirotherapy. Beyond these viral developments additional

mediators to radiovirotherapy alone would benefit in the future like TSH mediated (by recombinant TSH administration may be) would benefit. Classical radiovirotherapy did not achieve the success as expected but these additional modifications would probably increase the efficiency of the method and provide possible new applications in different cancer types. Combined treatment modalities are more preferable than single viral treatment like radiovirotherapy or as an adjunct to external beam treatment. Nuclear medicine treatments has harmony with viral treatments and additional to various different treating radionuclides (I-131, Re-188, At-11) imaging options also serves as a guide for treatment. A recent review has pointed that newer techniques may be developed like positron emission imaging of viral treatments [12]. Radioiodine treatment is the most efficient treatment modality among cancer therapeutics for differentiated thyroid tumors. If the effect of radioiodine treatment in other cancer types can be achieved by viral transfection this modality probably will be the best treatment option for most of the cancer types. However the effect of the treatment should be increased by some mediators and some definite solution for thyroidal uptake has to be determined.

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