Short history of fetal cell carcinogenesis

Thyroid cancer cells were believed to be generated by multi-step carcinogenesis, in which cancer cells are derived from thyrocytes, via multiple incidences of damage to their genome, especially in oncogenes or anti-oncogenes that accelerate proliferation or foster malignant phenotypes, such as the ability to invade the surrounding tissue or metastasize to distant organs, until a new hypothesis, fetal cell carcinogenesis, was presented. In fetal cell carcinogenesis, thyroid tumor cells are assumed to be derived from three types of fetal thyroid cell which only exist in fetuses or young children, namely, thyroid stem cells (TSCs), thyroblasts and prothyrocytes, by proliferation without differentiation. Genomic alterations, such as RET/PTC and PAX8-PPARγ1 rearrangements and a mutation in the BRAF gene, play an oncogenic role by preventing thyroid fetal cells from differentiating. Fetal cell carcinogenesis effectively explains recent molecular and clinical evidence regarding thyroid cancer, including thyroid cancer initiating cells (TCICs), and it underscores the importance of identifying a stem cells and clarifying the molecular mechanism of organ development in cancer research. It introduces three important concepts, the reverse approach, stem cell crisis and mature and immature cancers. Further, it implies that analysis of a small population of cells in a cancer tissue will be a key technique in establishing future laboratory tests. In the contrary, mass analysis such as gene expression profiling, whole genomic scan, and proteomics analysis may have definite limitations since they can only provide information based on many cells.

Key words: Thyroid cancer, Progenitor, Reverse approach, Stem cell crisis, Immature cancer
The risk of radiation-induced thyroid carcinoma increases in children approximately under age 5 but not in adults [10, 11]. Based on this evidence, thyroidologists recommend that adult patients with Graves’ disease undergo radioiodine therapy, since they will not suffer from radiation-induced thyroid cancer after the administration of $^{131}$I. High risk of radiation-induced thyroid cancer only in young children has been explained to be due to the high proliferation rate of thyrocytes in the young. However, the proliferation rate of thyrocytes remained constant from birth to age 10 and thyrocytes kept proliferating slowly, even in adults [12]. Thus, an evident discrepancy is observed between the proliferation rate of thyrocytes and cancer risk. Multi-step carcinogenesis in which thyroid cancer cells are derived from thyrocytes cannot explain this phenomenon.

From the molecular point of view, the main criticism of the classical model of multi-step carcinogenesis is that anaplastic carcinomas, which are described to be derived from differentiated carcinomas by accumulated damage to their genome, do not undergo the genetic alterations often observed in differentiated carcinomas. RET/PTC and PAX8-PPARγ1 rearrangements are observed in a high prevalence of differentiated carcinomas but they are not detected in anaplastic carcinomas [13, 14]. Furthermore, in five major studies carried out in Japan targeting patients with similar ethnic and environmental backgrounds, BRAF mutations were found in 39.7 % (378 out of 951) of papillary carcinomas, but only 18.1 % (6 out of 33) of anaplastic carcinomas, even though papillary carcinoma occupies about 90% of differentiated thyroid carcinoma in Japan [15-19].

These results suggest that thyrocytes may not be the origin of thyroid cancer cells, and thyroid cancer cells may not be generated by the de-differentiation of differentiated tumor cells. The simple interpretation of the above findings is that thyroid cancer cells are derived from something that only exists in the thyroid of young children but not adults, and the first event in carcinogenesis occurs in childhood and, due to the low proliferation rate of differentiated thyroid cancer cells, it takes a few decades before such cells form clinically detectable carcinomas. This speculation is supported by a recent observational trial of papillary thyroid microcarcinoma. In this study, the proportion of patients whose carcinomas showed enlargement by 3 mm was only 15.9 %, even at 10-year follow-up, which confirmed their slow growth [20].

**The basic concept of fetal cell carcinogenesis: a short cut to cancer cells**

One of the major drawbacks in the classical model of multi-step carcinogenesis is that it does not refer to the relationship between fetal cells including stem cells and carcinogenesis. This limits the origin of thyroid cancer to differentiated thyroid follicular epithelial cells. In multi-step carcinogenesis, a mature epithelial cell starts to de-differentiate and becomes a cancer cell accompanying the accumulation of multiple damages to its genome, resulting in the activation of oncogenes, inactivation of anti-oncogenes and acquisition of cancerous characteristics (Fig. 1).

In this model, a stem cell has to travel a very long road to produce a malignant tumor. However, we can find a short cut in this model. Developing fetal cells...
possess the ability of proliferation and migration, since such features are required in tissue development and remodeling. Their biological characteristics are quite similar to those of cancer cells. In fetal cell carcinogenesis, cancer cells are generated directly from fetal cells which already possess cancerous characteristics without undergoing further differentiation and de-differentiation processes. In other words, a cancer cell shows cancerous characteristics simply because they reflect the biological characteristics of the original fetal cell.

**Human fetal thyroid cells**

The above considerations revealed that we have to know more about fetal thyroid cells in order to understand thyroid cancer. Unfortunately, information on human thyroid fetal cells is still scarce. In a previous study, at least three types of fetal thyroid cells were observed [21]. The fetal thyroid is first recognized as a small number of cells expressing thyroid transcription factor-1 (TTF-1, *NKX2-1*) but not thyroglobulin (*TG*). Without evident proliferation, these cells move down from the lingual radix to the front neck. Even though it is not clear that these cells show pluripotency, we designated these cells as thyroid stem cells (TSCs) since thyroid development starts from these cells. TSCs soon become cells expressing *TG*, called thyroblasts. Thyroblasts do not form thyroid follicles and keep moving to the front neck, and the thyroid volume increases gradually due to the proliferation of thyroblasts. Next, fetal thyroid cells start forming follicles, but they do not produce thyroid hormone. Fetal thyroid cells during this period are called prothyocytes. Finally, after settling in the front neck, fetal thyroid cells turn into thyrocytes, then start producing thyroid hormone. Attention should be paid to the fact that thyroblasts show similarities to differentiated thyroid carcinoma cells in their high mobility and low growth rate.

**Fetal thyroid cell carcinogenesis**

Fig. 2 summarizes the basic concept of fetal thyroid cell carcinogenesis. Thyroid tumor cells are generated from the three types of fetal thyroid cells described above. Tumor cells derived from TSCs and thyroblasts possess cancerous characteristics, since they reflect the biological characteristics of their origin. Anaplastic carcinomas are derived from TSCs. Papillary and follicular carcinomas are mainly derived from thyroblasts. Follicular adenomas are derived from prothyocytes, which do not possess cancerous characteristics. In previous papers, follicular carcinomas were described to be derived from prothyocytes [2-5]. The present model has two advantages over the previous model. First, it is clear why follicular carcinomas possess cancerous characteristics. Second, the rarity of follicular carcinomas compared to papillary carcinomas and follicular adenomas is well explained when we hypothesize that both papillary and follicular carcinomas originate from thyroblasts but follicular carcinomas are a more differentiated variant of papillary carcinoma.

Any events that prevent fetal thyroid cells from differentiation can be a cause of cancer. It is suggested that *RET/PTC* and *PAX8-PPARγ1* rearrangements and mutations in *BRAF* contribute to such events. In this model, these oncogenes act as an initiation but not promotion factor in thyroid carcinogenesis, which indicates that, unlike the classical multi-step carcinogenesis model in which activation of oncogenes is inevitable in tumor progression, this model does not assure the tumor suppression effect of the inhibitors against these oncogenes. Fetal cell carcinogenesis regards carcinogenesis as an abnormal development of fetal thyroid cells.
Reverse approach

If tumor cells reflect the nature of their corresponding fetal cells, then we can estimate the biological characteristics of fetal thyroid cells using the evidence obtained from thyroid tumors. For example, we can estimate the existing period of each predicted fetal thyroid cell.

Fetal thyroid cells, especially TSCs and thyroblasts, are not likely to exist abundantly in the thyroid in adults, since the adult thyroid does not usually regenerate after partial thyroidectomy [22]. No induction of thyroid carcinomas by radiation in adults supports this assumption [11]. After the Chernobyl accident, pediatric papillary carcinoma was most frequent at age 0 at the time of the accident, and the frequency rapidly decreased until age 5 [10]. Follicle formation, which is a sign of the dominant existence of prothyrocytes, is first observed at approximately the 10th gestational week [23]. These data suggest that thyroblasts are dominant up to the 10th gestational week, and then their number rapidly decreases, resulting in almost complete loss at age 5.

The period of the existence of TSCs is not clear. However, when considering that no pediatric anaplastic carcinoma was reported after the Chernobyl accident, it is likely that TSCs disappear or stop producing thyroblasts in the very early stage of pregnancy before the fetal thyroid starts iodine uptake [10]. Remnants of TSCs might rarely exist in adults and this explains the rarity of anaplastic carcinoma.

The finding that no follicular carcinoma was observed after the Chernobyl accident should be discussed from a different aspect [10]. In fetal cell carcinogenesis, both papillary and follicular carcinomas are derived from thyroblasts but the latter are regarded as more differentiated variants. As well known, the causes of these two carcinomas are basically different, for example, the RET/PTC rearrangement and the BRAF mutation are restricted in papillary carcinomas while the PAX8-PPARγ1 rearrangement is restricted in follicular carcinomas. Thus, the rarity of follicular carcinoma is not surprising if genetic alterations caused by irradiation transformed fetal cells favorably into papillary carcinomas but not follicular carcinomas. In fact, no radiation-induced tumor with the PAX8-PPARγ1 rearrangement has been reported after the Chernobyl accident.

Prothyrocytes appear around the 10th gestational week, when the formation of follicles is first observed. Since they are derived from thyroblasts, they continue to exist at least until age 5. It is not clear, however, until when prothyrocytes persist, because these cells show morphological similarity, such as follicle formation.

In a similar manner, we can estimate marker genes to identify these fetal cells (Table 1). TTF-1 (NKX2-1) is expressed in all three types of fetal thyroid cells. Thyroblasts and prothyrocytes express TG. A fetal protein, oncofetal fibronectin (onfFN) is a splicing variant of normal fibronectin, and it is expressed in various fetal tissues in the early stage of development [24]. Expression of onfFN is observed restrictedly in anaplastic carcinoma and papillary carcinomas and its weak expression is observed in some follicular carcinomas [25-28], thus, it is speculated that onfFN is expressed in TSCs and thyroblasts, which exist in the early phase of thyroid development.

TFF3 is a relatively new family of peptides that bear a three-loop trefoil domain [29]. The function of TFF3 peptide in the thyroid is still unknown; however, abundant expression in various ulcerative conditions suggests an important role in mucosal defense and repair during thyroid hormone production. TFF3 mRNA is expressed in normal thyroid and follicular adenoma, whereas its decrease expression is observed in anaplastic, papillary and follicular carcinomas [30, 31]. Thus, TFF3 is a candidate gene to differentiate prothyrocytes from thyroblasts.

Trefoil factor 3 (TFF3) is a relatively new family of peptides that bear a three-loop trefoil domain. If tumor cells reflect the nature of their corresponding fetal cells, then we can estimate the biological characteristics of fetal thyroid cells using the evidence obtained from thyroid tumors. For example, we can estimate the existing period of each predicted fetal thyroid cell.

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The most difficult distinction is thyrocytes from prothyrocytes, since prothyrocytes are well-differentiated cells and the only difference between thyrocytes and prothyrocytes is their proliferation and hormone production ability. In fetal cell carcinogenesis, prothyrocytes are suggested to be the origin of highly differentiated tumors, such as hyperfunctioning adenomas. Thus, genes expressed exclusively in hyperfunctioning adenomas, for example, N-cadherin (CDH2), are suggested to be candidate marker genes for prothyrocytes [32].

| Table 1 Predicted molecular markers expressed in fetal thyroid cells |
|---|---|---|
| fetal thyroid cell | corresponding tumor | molecular marker |
| TSC | anaplastic carcinoma | NKX2-1, onfFN |
| thyroblast | papillary carcinoma | NKX2-1, TG, onfFN |
| prothyrocyte | follicular carcinoma | NKX2-1, TG, CDH2, TFF3 |
| thyrocyte | follicular adenoma | NKX2-1, TG, TFF3 |
Experimental evidence that supports fetal cell carcinogenesis

Jhiang et al. found that RET/PTC1 transgenic mice developed thyroid papillary carcinoma and congenital hypothyroidism due to their lack of normal thyroid cells [33]. Charles et al. bred mice with thyrocyte-specific expression of mutated BRAF [34]. These mice also developed thyroid papillary carcinoma and hypothyroidism. In these mice, pharmacologic inhibition of mutated BRAF signal led to restoration of thyroid follicular cells and hormone production, suggesting that papillary carcinoma cells differentiated into thyroid follicular cells.

There results suggested that thyroid cancer cells are produced with a single hit in their genome, and such an effect is reversible since cancer cells can revert to normal cells. These features of thyroid carcinoma are quite different from those described in multi-step carcinogenesis, in which cancer cells are generated by initiation and progression with multiple damage to their genome. In the fetal cell carcinogenesis theory, hypothyroidism due to the lack of normal thyroid follicular cells occurs eventually in these mice if the RET/PTC1 or mutated BRAF prevents the differentiation of fetal thyroid cells into thyrocytes. The cells observed in these transgenic mice might not be thyroid papillary carcinoma cells, but might be fetal thyroid cells. It is also interesting that the induction of thyroid carcinomas by expressing oncogenes in the thyroid is only possible when they are introduced in fetal mice [35].

Todaro et al. found that the tumorigenic capacity in differentiated thyroid cancer is confined to a small sub-population of stem-like cells with high aldehyde dehydrogenase (ALDH) activity [36]. These cells can be regarded as thyroid cancer-initiating cells (TCICs) and, due to their high tumorigenic activity and poorly differentiated features, their origin are suggested to be TSCs. An interesting result of this experiment is that these stem-like cells developed into differentiated thyroid tumor cells expressing TG when they formed tumors in nude mice. These results indicated that in the thyroid, ALDH-negative components in thyroid tumors have only limited proliferation ability, thus tumors are mainly formed by the proliferation of undifferentiated TCICs into differentiated cells, which is suggested in the fetal cell carcinogenesis hypothesis.

Fetal cell carcinogenesis and clinical features of thyroid cancer

Thyroid tumors are common in middle-aged women [37]. In fetal cell carcinogenesis, the origins of thyroid carcinomas are fetal thyroid cells existing mainly during the gestational period. Thus, fetal thyroid cells are likely to favor an environment exposed to estrogen, which explains the higher prevalence of differentiated thyroid tumors in women than men. On the other hand, undifferentiated carcinomas are not likely to be sensitive to estrogen since they are derived from undifferentiated fetal cells that exist only in the early gestational period when maternal estrogen remains at a low level. This explains why these tumors do not show an evident sex difference. Furthermore, their poor ability to concentrate iodine due to the loss of expression of some differentiation markers such as sodium/iodide symporter (NIS) or thyrotropin receptor can be explained that they reflect the characteristics of originating fetal cells [38]. Differentiated thyroid carcinomas generally show a favorable prognosis, since they show slow growth, whereas local or distant metastases are observed at high frequency. These features link directly to those of fetal thyroid cells, especially thyroblasts, which proliferate slowly but migrate rapidly. Papillary thyroid microcarcinomas are observed in a high prevalence of up to 30% of autopsied cases [39]. At least some of these cells may not be carcinomas, but the remnants of thyroblasts.

One of the distinguishing features of thyroid cancer is its favorable prognosis in the young [40]. In multi-step carcinogenesis, poor prognosis in the elderly is explained to be due to genomic damages accumulated in cancer cells after many years of proliferation, enabling cancer cells to acquire more aggressive characteristics. However, this hypothesis is not convincing since thyroid cancers in the young cause invasion or metastasis in a similar manner to those in the elderly [41]. Thyroid carcinomas in the young seem to be self-limiting, even though invasion or metastasis is observed frequently. In fetal cell carcinogenesis, two types of differentiated carcinoma are suggested: One contains TCICs (immature cancer) and the other does not contain (mature cancer) (Fig. 3). TCICs, which express stemness characteristics, are possibly derived from TSCs. Tumor cells derived from thyroblasts start proliferating immediately but slowly, whereas those derived from TSCs tend to stay quiescent for a while. Thus, tumors derived from
thyroblasts become clinically evident earlier than those from TSCs. This speculation is supported by the fact that anaplastic carcinomas, which are thought to be derived from TSCs in fetal cell carcinogenesis, are observed only in the elderly. Clinically evident thyroid differentiated carcinomas are a mixture of mature and immature cancers. Mature and immature cancers show favorable and poor prognosis, respectively, since while mature cancers are self-limiting, immature cancers undergo unlimited proliferation supported by the self-renewal activity of TCICs. This model explains the favorable prognosis of thyroid cancer in the young, since the ratio of immature cancers with a poor prognosis increases in an age-dependent manner.

Even though the above consideration suggests the importance of differentiating these two types of cancers, it is not possible using the present pathological diagnosis, since TCICs exist as a minor cell population in tumor tissues. Analysis using flow cytometry might be able to detect TCICs [36]. However, such analysis may not be applied to the majority of the tumor samples, because it is quite laborious and, in addition, it needs a large sample volume.

Some questions remain to be clarified in the fetal cell carcinogenesis theory

Although many questions raised by multi-step carcinogenesis are well explained in the fetal cell carcinogenesis hypothesis, some remain to be clarified. In fetal cell carcinogenesis, TSCs and thyroblasts usually disappear before adolescence. Then, why do anaplastic carcinomas, which are derived from them, occur only in the elderly? [42] If anaplastic carcinomas are generated from fetal thyroid cells, their origin must be TSCs, since stem cells are the only cells, except cells with a special function such as germ cells, myocardocytes and neurons, that are able to remain alive for many years without proliferation [43]. Furthermore, the coexistence of a differentiated component is not surprising, since TSCs have the ability to generate thyroblasts and prothyrocytes. When TSCs generate thyroblasts or prothyrocytes, the proliferating tumors act as differentiated tumors, whereas when TSCs themselves start to proliferate, the resulting tumor acts as an undifferentiated carcinoma and is recognized as an anaplastic transformation. One possible explanation for their sudden proliferation in the elderly is that TSC remnants cannot maintain the characteristics of a stem cell after many years of repeated proliferation, and begin uncontrolled proliferation as undifferentiated tumor cells, like a time-bomb (stem cell crisis). However, the fate of aged stem cells is not well known and is still controversial. Some studies have reproduced stem cell crisis in vitro, but they have not been confirmed because such experiments include many technical obstacles [44-46].

Some biological characteristics, such as genomic instability, preventing apoptosis, and escaping from checkpoints, can be observed only in cancer cells but not in fetal cells [47]. Cancer cells are likely to acquire these characteristics during the progression stage, but it is difficult to describe the precise mechanism in the fetal cell carcinogenesis hypothesis at present. These difficulties in the fetal cell carcinogenesis hypothesis are mainly due to the fact that the precise relationship between fetal cells and carcinogenesis has not yet been fully clarified. Accumulated information on fetal cells, especially stem cells, according to advances in fetal cell science, may answer these questions in the near future.

Although thyroid cancers are derived from fetal cells in fetal cell carcinogenesis that already exist in the thyroid of the fetus, the increased risk of thyroid cancer after in utero exposure has not been reported, which shows a clear discrepancy from newborn infants
Fetal thyroid cell carcinogenesis

two types of fetal thyroid cells are likely to exist in the thyroid of the young and they control the volume and function of the thyroid. In multinodular goiter, multiple nodules, degenerated regions and cysts are observed in the thyroid. In the majority of cases, thyroid hormone stays within the normal range. Although the prevalence of this disease is relatively high, its exact pathogenesis is not clear, except in rare cases that accompany inherited defects in thyroid hormone synthesis [51]. Since many proliferative focuses are observed, some kinds of defect in thyroid regeneration might be the cause of this disease and the role of fetal thyroid cells, which are responsible for proliferation, is of interest. Thomas et al. isolated cells expressing stemness genes from nodular goiters and concluded that they are thyroid stem cells [52]. However, their results need more careful interpretation, since these cells were analyzed after culture for a relatively long period under non-physiological conditions.

T3-predominant Graves’ disease is a Graves’ disease observed in some young patients. It is characterized by a large goiter, an unfavorable clinical course, and an increased level of serum T3 compared to T4. This increase was proven to be caused by T4 to T3 hyperconversion by iodothyronine deiodinases in thyroid follicular cells [53]. Some recent studies reported an interesting similarity in gene expression between tissues from T3-predominant Graves’ disease and hyperfunctioning adenomas. They overexpress not only iodothyronine deiodinases but also N-cadherin (CDH2) [54, 55]. If T3 predominate Graves’ disease is caused by an increased number of fetal thyroid cells, probably prothyrocytes, some clinical features of T3-predominant Graves’ disease, such as its high prevalence in the young and tendency to form a large goiter, are easily explained. Tissue from T3-predominant Graves’ disease might be a good material to identify fetal thyroid cells.

As discussed above, fetal thyroid cells might play a significant role in other thyroid diseases besides cancer [10]. Considering that the introduction of oncogenes into the thyroid of the fetus caused carcinoma at birth, some other unknown factors, such as the distribution of radioactive iodine, is likely to take part in this discrepancy [33].

Cancer stem cell and fetal cell carcinogenesis

Cancer stem cells (CSCs) are defined as cancer cells persisting in tumors as a distinct population that possess characteristics associated with normal stem cells, and CSCs may generate tumors through the stem cell processes of unlimited proliferation, self-renewal and differentiation into multiple cell types [43]. Such cells have been found in many types of cancer tissue and types and they are believed to cause relapse and metastasis by giving rise to new tumors. There are some confusing descriptions about the relationship between fetal cell carcinogenesis and CSC theories [8]. In previous papers, CSCs were not directly referred to in the fetal cell carcinogenesis hypothesis [2-5]. Tumor cells derived from TSCs or TCICs may be regarded as the analogue of CSCs. However, in fetal cell carcinogenesis, TSCs or TCICs play some roles only in the early phase of thyroid development. Since thyroid tumors contains various histological subtypes derived from many types of cells with different stages of differentiation, the entire mechanism of thyroid carcinogenesis cannot be explained only with TSCs or TCICs. Thus, at least in the thyroid, the CSC theory alone is not sufficient to explain carcinogenesis.

CICs appear to be important players not only in fetal cell carcinogenesis but also in multi-step carcinogenesis [48-50]. However, there is a fundamental difference in their nature. In fetal cell carcinogenesis, CICs are generated from undifferentiated fetal cells, mainly stem cells, by preventing their differentiation, and the nature of CICs is a mirror image of their original fetal cells. In contrast, in multi-step carcinogenesis, CICs are generated from stem cells by malignant transformation by accumulating damage in their genome, resulting in the acquisition of numerous malignant characteristics. Thus, CICs are transformed cells whose nature is quite different from stem cells.

Thyroid disease as fetal cell disease

An interesting fact that arises from the reverse approach is that not only thyrocytes, but at least one or two types of fetal thyroid cells are likely to exist in the thyroid of the young and they control the volume and function of the thyroid. In multinodular goiter, multiple nodules, degenerated regions and cysts are observed in the thyroid. In the majority of cases, thyroid hormone stays within the normal range. Although the prevalence of this disease is relatively high, its exact pathogenesis is not clear, except in rare cases that accompany inherited defects in thyroid hormone synthesis [51]. Since many proliferative focuses are observed, some kinds of defect in thyroid regeneration might be the cause of this disease and the role of fetal thyroid cells, which are responsible for proliferation, is of interest. Thomas et al. isolated cells expressing stemness genes from nodular goiters and concluded that they are thyroid stem cells [52]. However, their results need more careful interpretation, since these cells were analyzed after culture for a relatively long period under non-physiological conditions.

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Fetal cells enter the maternal circulation during pregnancy and can persist in the maternal blood or tissues for decades, creating a fetal cell microchimerism. In the thyroid, Cirello et al. found male cells expressing TG in tumor and normal tissues in women with papillary carcinoma [56]. The pathological significance of these cells is not clear; however, the possibility remains that these cells exert a pathogenetic mechanism in not only tumor formation but also autoimmunity, such as Hashimoto’s disease or Graves’ disease.

As discussed above, fetal thyroid cells might play a significant role in other thyroid diseases besides can-
cancer. More information on fetal thyroid cells in the near future may reveal unexpected insights into various thyroid diseases, and then fetal cell carcinogenesis will be regarded as a spearhead of such methods of consideration.

Is cancer Godzilla or a coelacanth?

Godzilla is a giant brutal monster in a movie. It was originally a small, innocent creature but was transformed by radiation from an atomic bomb. Cancer cells in the classical model of multi-step carcinogenesis looks exactly like this, and a super-weapon is needed to defeat them. In contrast, in fetal cell carcinogenesis, a cancer cells looks like a coelacanth, an ancient fish that survived for 400 million years. Even though its appearance differs greatly from those of other fish, it has not undergone transformation, but has remained the same for many years, while other fish have undergone gradual changes to their morphology. In fetal cell carcinogenesis, a cancer cell mimics a fetal cell, and as described in the stem cell crisis, even an aged stem cell might be a major source of malignant tumors. The definite distinction between fetal cells and cancer cells is often difficult, and in such a case, an attack with a “super-weapon” is not likely to be effective.

The basic concept of fetal cell carcinogenesis represents the serious fate of humans. Stem cells are inevitable in tissue regeneration and loss of stem cells results in death by old age. On the other hand, persistence of aged stem cells leads to death from cancer. It is clear that humans are definitely mortal beings. In order to control cancer, we have to control stem cells, the regulation of which may lead to an attempt to achieve immortality. The difficulty of beating cancer may come from this profound issue.

In the case of thyroid cancer, however, we can foresee an optimistic future. In fetal cell carcinogenesis, thyroid cancers, especially immature cancers, which often result in death from cancer, arise from the remnants of undifferentiated fetal thyroid cells, especially TSCs. In other words, those who have a risk of future death from thyroid cancer have a remnant of undifferentiated fetal cells in their thyroid. If we can establish a method to screen in vivo for such a remnant in adults and identify its exact localization inside the thyroid, fetal thyroid cells can be eliminated easily by percutaneous ethanol injection therapy (PEIT), and then there will be no more deaths from thyroid cancer since its origin can be eliminated. Thus, the most important project to overcome thyroid cancer might be the establishment of a laboratory test detecting a small number of undifferentiated components among thyroid tissues using flow cytometry is now underway [57].

References


