Structure and expression of c-myc and c-fos proto-oncogenes in thyroid carcinomas

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Proto-oncogenes are thought to have regulatory roles in normal cell proliferation and differentiation. They may contribute to neoplastic transformation when there is an alteration in their function (Barbacid, 1986; Alitalo & Schwab, 1986; Cory, 1986). The two proto-oncogenes c-myc and c-fos, which encode nuclear proteins, seem to have a crucial role in the control of cell proliferation. When quiescent fibroblasts are stimulated by peptide growth factors, c-fos and c-myc genes are rapidly and transiently induced (Müller et al., 1985; Verma et al., 1985). Studies of c-fos expression in a variety of cell types and tissues at different stages of development have suggested that the c-fos gene product may play a role in cell differentiation (Müller et al., 1985; Verma et al., 1985; Müller, 1986; Gonda & Metcalf, 1984). However, the characterization of the c-fos gene has only been carried out in a small number of fresh human cancers (Mavilio et al., 1986; Lehn et al., 1986). By contrast, the c-myc gene was found to be rearranged, amplified and overexpressed in a wide variety of human cancers (Alitalo & Schwab, 1986; Riou et al., 1984; Rothberg et al., 1984; Riou et al., 1985, 1987; Guerin et al., 1985; Erisman et al., 1985; Terrier et al., 1985). It was shown to be involved in the progression of various cancer (Barbacid, 1986; Little et al., 1983) in particular in cancers of the cervix (Riou et al., 1985, 1987), in which this oncogene is more frequently amplified and overexpressed in the more advanced stages (III and IV) than in the earlier ones (I and II).

Long term prognosis of thyroid carcinoma is favourable, but is modulated by several parameters such as age, histologic characteristics, sex (Tubiana et al., 1985). The EORTC prognostic index is a weighted factor which takes into account most of these parameters (Byar et al., 1979). A pilot study (Terrier et al., 1985) showed that in one patient with thyroid carcinoma, there was an overexpression of the c-myc gene in the anaplastic component, in accordance with the severe prognosis of this histologic type; in contrast, the expression of this oncogene was normal in the papillary component. This prompted us to characterize the c-myc and c-fos proto-oncogenes in thyroid carcinomas and to analyze their expression in relation to prognosis and differentiation (Schlumberger et al., 1980, 1986).

Materials and methods

Tissue specimens

Tissue specimens were obtained at thyroidectomy and immediately frozen in liquid nitrogen. They consisted of 23 specimens of primary thyroid cancers. In 4 of these patients metastatic lymph nodes were also obtained (Table I); 33 non malignant thyroid samples were studied as controls (22 adenomas, 3 Graves' disease, 8 normal thyroid glands). Histological examination of a part of the specimens by frozen sections allowed the selection of the pathologic part of the thyroid tissue without normal tissue. Thyroid tissues were histologically classified according to the WHO classification (Heidinger & Sobin, 1974).

Isolation of RNA and DNA

RNA and DNA were extracted from the same tissue sample corresponding to about 50–200 mg of fresh tissue. Frozen tissues were ground in liquid nitrogen and nucleic acids were isolated as previously described (Barbacid, 1986). Total RNAs were also analyzed. Elevated levels of the two proto-oncogenes were detected in 9/22 (41%) of the cancer patients, respectively. High levels of c-myc transcripts were more frequently found in thyroid carcinomas with unfavourable prognosis. Concomitant elevated levels of both c-myc and c-fos RNAs were found in 8 cancers. High levels of c-myc RNA were also found in 1 out of 22 specimens of adenoma, in 1 specimen of Graves' disease and in 2 normal thyroid glands. High levels of c-fos RNA were found in 20 of the 22 adenoma samples and in 2 out of 8 normal thyroid tissues. These data indicate that the overexpression of c-myc and c-fos genes is independent of an alteration of the loci. The high levels of c-fos found in adenoma may be associated with the differentiation state of these tumours.

Table I Expression of c-myc and c-fos proto-oncogenes in human thyroid carcinomas

| Histological type of thyroid specimens | No. of patients with elevated levels of c-onc RNA* | No. of patients analyzed |
|---------------------------------------|--------------------------------------------------|-------------------------|
| c-myc RNA                             | c-fos RNA                                        |
| Carcinomas                            |                                                  |
| Follicular well differentiated         | 0/1                                              | 1/1                     |
| Follicular moderately differentiated   | 4/6                                              | 3/6                     |
| Papillary                             | 6/13                                             | 7/13                    |
| Anaplastic                            | 1/1                                              | 1/1                     |
| Medullary                             | 2/2                                              | 2/2                     |
| Total                                 | 13/23                                            | 14/23                   |
| Benign tissues                        |                                                  |
| Adenoma                               | 1/22                                             | 20/22                   |
| Graves' disease                       | 1/3                                              | 0/3                     |
| Normal thyroid tissues                | 2/8                                              | 2/8                     |

*Elevated levels of c-myc and c-fos transcripts corresponding to ≥3 fold the levels found in normal human tissues and cells (thyroid, lymphocytes).
previously described dried and Nitrocellulose to endonuclease(s) applied two Slotblots described al., Sample exon transcription of probes specific allow used Northern blot and DNA normal and single in phoresis the same densitometer determine signal intensity in a 1.2% Kodak films. The The blots were prehybridized, blots. The probes were labelled by $^{32}$P-dCTP (3000 Ci mmol$^{-1}$) to a specific activity of 2-5 x 10$^8$ cpm µg$^{-1}$ according to the nick-translation technique (Maniatis et al., 1982).

Quantitative analysis of the c-myc and c-fos proto-oncogenes

The copy number of c-myc and c-fos proto-oncogenes in DNA samples was evaluated by microdensitometer tracings of autoradiograms. The $\beta_1$ globin pseudogene was taken as a single copy gene internal control (Little et al., 1983) and used to estimate the copy number of the oncogenes in normal and tumour tissues. This method has been shown to allow a reliable quantitative measurement of copy numbers.

Quantitative analysis of the c-myc and c-fos gene expression

The expression of proto-oncogenes was analyzed by Northern blot and Slot blot hybridization of total RNA. The same blots were washed off for oncogene signals and rehybridized to a murine actin probe (Alonso et al., 1986). The signal intensity obtained with actin probe was the same in each slot blot providing a control for RNA quality and content among samples. The integrity and amount of total RNA of each sample was measured by a preliminary electrophoresis in a 1.2% mini agarose gel after ethidium bromide staining. Amounts of c-myc transcripts were determined by densitometer tracings of autoradiograms at different exposure times. The c-myc RNA of N417 cells was used to determine the levels of transcripts in thyroid RNA, considering that the levels of c-myc RNA in those cells correspond to ~30 fold the level found in normal cells (Little et al., 1983). Carcinomas were considered as overexpressed when the c-myc RNA level was found to be $\geq$3 times the level found in normal cells.

**EORTC prognostic index**

The EORTC prognostic index for thyroid carcinoma (Byar et al., 1979) is a simple scoring system obtained by adding to the age at diagnosis (in years), 12 if male, 10 if medullary or follicular moderately differentiated, 45 if anaplastic, 10 if tumour extended beyond the thyroid gland (T3 category), 15 if there is at least one distant metastatic site and 15 in addition to above if there are multiple distant metastatic sites. Regional lymph node status is not taken into account in this model.

**Results**

The c-myc and c-fos loci were characterized in 12.5 and 9.0 kb DNA bands respectively, as expected for human DNA (Figure 1) (Müller et al., 1985; Verma et al., 1985; Riou et al., 1984). The human $\beta_1$ globin pseudogene was detected in a 7.2 kb DNA band. No significant amplification was found in carcinoma samples nor in other thyroid specimens. No rearrangement was detected using DNA cleavage by several restriction enzymes (HindIII, PvuII, ClaI, XbaI). Furthermore, DNA recovered from lymph node metastases in 4 of these patients provided no evidence of gene amplification or gene rearrangement.

Total RNAs were analyzed for the expression of c-myc and c-fos proto-oncogenes by Northern blot hybridization. Transcripts of 2.4 kb and 2.2 kb were detected with c-myc and c-fos probes respectively in all specimens of thyroid carcinoma, adenoma, Graves’ disease and normal thyroid glands (Figure 2). Two minor bands with a migration close to that of 18S and 28S ribosomal RNAs were occasionally detected. Furthermore 13 of the 23 thyroid carcinomas exhibited high levels of c-myc RNA (Table 1) corresponding to ~3-to-20 fold the level observed in normal human tissues (lymphocytes, thyroid) (Figure 3). The c-myc RNA levels were elevated in the 4 lymph node metastases as well as in the corresponding primary tumours. It was at high levels in 9 of the 18 tumours with lymph node metastases and in 3 out of the 5 tumours without lymph node metastases. Elevated c-myc RNA levels were also found in 1 out of 22 specimens of adenoma, 1 out of 3 Graves’ disease and 2 out of 8 normal thyroid tissues.

Fourteen of the 23 thyroid carcinomas exhibited high levels of c-fos RNA. An overexpression of both c-fos and c-myc genes was found in 8 carcinomas. High levels of c-fos transcripts were found in 20 of the 22 adenomas and in the two normal thyroid tissues which contained also high levels of c-myc RNA.

A relationship has been sought between the overexpression of these oncogenes and the prognosis of the cancer patients by using the EORTC prognostic index (Byar et al., 1979). The c-myc gene was ~2 times more frequently overexpressed, in patients with an unfavourable EORTC prognostic index, than in those with a favourable index ($p=4.79$ P<0.03) (Tables II and III). In contrast, the expression of the c-fos gene was not related with this index or with the regional lymph node status (Table III). No relationship was found between the expression of these two oncogenes on the one hand, and either the functional characteristics of the neoplastic tissues such as the capacity of radioidine uptake, or previous TSH stimulation (surgery during thyroxin treatment or after TSH stimulation), on the other (Table II).
The lymph gland DNA was digested to 9.0 kb band. The c-myc gene was revealed in the 12.5 kb band and β₂ globin pseudogene in the 7.2 kb band. a, normal thyroid gland; d, lymphocytes; e to k, thyroid carcinomas. Amplification of c-myc gene was observed in N417 cells, while no amplification was detected in the other tissues. Blot was exposed to Kodak XAR5 film for 48 h.

(B) The c-myc and β₂ globin signals of blot presented in panel A were washed off and the blot rehybridized with 32P-labeled v-fos probe (BglII-BglII fragment). The c-fos gene was revealed in the 9.0 kb band.

Sizes of DNA bands were calculated using φ1phage DNA cleaved with HindIII endonuclease as standard.

Discussion

The present data clearly demonstrate that in fresh thyroid tissues, either normal or with various benign or malignant conditions, the structure of c-myc and c-fos proto-oncogenes is not altered and that these genes are neither amplified nor rearranged. Moreover no alteration was observed in the four lymph node metastases.

The c-myc and c-fos gene transcripts from normal or malignant tissues migrate as expected for human RNA (Verma et al., 1985; Müller et al., 1986; Gonda & Metcalf, 1984). These data are at variance with the recent description of three distinct myc transcripts on a smaller number of patients studied (Yamashita et al., 1986). High levels of c-myc transcripts corresponding to about 3-to-20 fold the normal level were detected in 13 of the 23 thyroid carcinomas. c-myc overexpression was found two times more frequently in patients with unfavourable prognostic indicators than in those with a favourable prognostic index in accordance with what has been demonstrated in carcinomas.
Unexpectedly, however, in several studies, the expression of c-myc and c-fos genes was found to be elevated in normal tissues, which suggested that these genes play a role in neoplastic transformation. Furthermore, it was suggested that the expression of c-myc and c-fos genes is not simply a marker of proliferative activity but reflects additional tissue-specific gene regulation operating during normal embryogenesis (Pfeiffer-Ohlsson et al., 1985). Several papers have shown that the high levels of c-myc RNA observed in some cell lines do not correspond to an overexpression of the c-myc gene but rather to a greater stability of the c-myc transcripts (Dani et al., 1984; Rabbits et al., 1985). In the present study such a mechanism cannot be ruled out.

In one patient, the c-fos gene was overexpressed in the analaplastic component, while c-fos RNA levels were normal in the papillary component surrounding the analaplastic tissue. This result was unexpected since c-fos overexpression was shown to be associated with differentiation in cell systems (Müller et al., 1985; Verma et al., 1985; Müller, 1986). The role of c-fos in thyroid tissue remains to be elucidated since markedly elevated levels were also found in adenomas; in these tissues the hypothesis that c-fos may accompany the differentiation state of these cells cannot be ruled out. The regulation of c-myc and c-fos proto-oncogenes in normal thyroid tissues at different stages of differentiation is still unknown. It is therefore difficult to assess whether this overexpression can play a role in tumorigenesis; low levels of c-fos expression are associated with the transformation of fibroblasts whereas the c-fos proto-oncogene is highly expressed in some normal cells, for example in mature macrophages and in normal amniotic cells (Müller, 1986; Gonda & Metcalfe, 1984). The histological observation of thyroid sections show that tumoural as well as normal tissues are weakly associated with macrophages, eliminating the participation of these cells in the oncogene expression. In cell lines, the regulation of c-fos expression is complex (Greenberg et al., 1986) and is modulated by external signals (Müller et al., 1986). It is not known whether the high levels of transcripts are associated with high levels of protein expression as interestingly discussed for cervical cancers (Hendy-Ibbes et al., 1987). A better understanding of the significance of these oncogene expressions in thyroid cancer requires further fundamental research; however the present data already underline the frequent existence of an overexpression of c-myc in the most malignant thyroid cancer, but it is not clear whether this dysregulation of the c-myc expression is the cause or the consequence of this malignancy.

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Table II  Clinical data of patients with thyroid carcinoma and transcription of c-myc and c-fos oncogenes

| Patient no. | Age | Sex | Histological type | EORTC Lymph node index | TSH stim. | 131I uptake | Levels of transcripts |
|-------------|-----|-----|-------------------|------------------------|----------|------------|---------------------|
|             |     |     |                   |                        |          |            | c-myc | c-fos |
| 1           | 62  | M   | Anap              | 129                    | +        | -          | >5     | >5   |
| 2           | 69  | M   | FMD               | 121                    | +        | -          | 1      | 1    |
| 3           | 57  | M   | MTC               | 111                    | -        | ND         | >5     | >5   |
| 4           | 57  | F   | FMD               | 117                    | -        | +          | >5     | >5   |
| 5           | 71  | F   | FMD               | 111                    | +        | +          | 5      | 1    |
| 6           | 63  | M   | Pap               | 85                     | +        | +          | 5      | 1    |
| 7           | 35  | M   | FMD               | 82                     | +        | +          | >5     | 5    |
| 8           | 57  | M   | FMD               | 79                     | -        | ND         | 4      | 5    |
| 9           | 64  | F   | Pap               | 64                     | +        | +          | 1      | 1    |
| 10          | 22  | M   | Pap               | 64                     | +        | +          | 1      | 1    |
| 11          | 18  | F   | FMD               | 58                     | +        | +          | <1     | 1    |
| 12          | 57  | F   | Pap               | 57                     | -        | ND         | 3      | 5    |
| 13          | 56  | F   | Pap               | 56                     | -        | ND         | 1      | 5    |
| 14          | 37  | F   | MTC               | 47                     | +        | -          | >5     | >5   |
| 15          | 33  | M   | Pap               | 45                     | +        | -          | 1      | >5   |
| 16          | 32  | F   | Pap               | 42                     | +        | -          | 1      | 1    |
| 17          | 26  | F   | Pap               | 36                     | -        | -          | >5     | 5    |
| 18          | 25  | F   | Pap               | 35                     | +        | +          | 1      | 3    |
| 19          | 22  | M   | FWD               | 34                     | -        | ND         | 1      | 5    |
| 20          | 33  | F   | Pap               | 33                     | +        | +          | 3      | 1    |
| 21          | 27  | F   | Pap               | 27                     | +        | ND         | >5     | 1    |
| 22          | 12  | M   | Pap               | 24                     | +        | +          | 3      | 1    |
| 23          | 22  | F   | Pap               | 22                     | +        | -          | 1      | >5   |

*Anap: anaplastic; FMD: follicular moderately differentiated; FWD: follicular well differentiated; Pap: papillary; MTC: medullary thyroid carcinoma. c-myc and c-fos levels were evaluated by comparison to levels found in normal tissues, taken as level 1.

Table III  c-myc and c-fos expression as a function of the EORTC prognostic index (Byar et al., 1979)

| EORTC prognostic index | No. of patients | No. of patients with elevated transcripts of |
|------------------------|-----------------|-------------------------------------------|
|                        |                 | c-myc | c-fos |
| ≥66                    | 8               | 7     | 5    |
| ≤65                    | 15              | 6     | 9    |

*4 patients died within 10 months after oncogene analysis; All the patients of this series were still alive.
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