Letter

# FISH and immunohistochemical status of the hepatocyte growth factor receptor (c-Met) in 184 invasive breast tumors

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In their report, Götte and coworkers [1] analyzed the expression of c-Met in 200 patients with ductal carcinoma *in situ*. They concluded that c-Met could be related to angiogenic and lymphangiogenic factors in ductal carcinoma *in situ*. On the other hand, Greenberg and coworkers [2] studied 31 patients with ductal infiltrating carcinoma (DIC) to detect c-Met expression in their axillary fluids. They observed a correlation of c-Met expression with increasing tumor size and grade, capillary and lymphatic invasion and lymph node metastasis.

We applied the fluorescent *in situ* hybridization (FISH) technique using the LSI D7S486/CEP7 commercial probe (Abbott Molecular Inc., Des Plaines, IL, USA), which includes the *MET* gene, and immunohistochemistry using c-Met monoclonal antibody clone 3D4 (Invitrogen, Carlsbad, CA, USA) to 184 archival invasive breast tumors (93 DIC and 91 lobular carcinomas). We constructed ten tissue microarrays with three replicates per sample. Pearson's chi-squared and Fisher's exact test were used to analyze the results.

None of the 155 breast tumors analyzed by FISH presented amplification of *MET* and 35 cases (22%) had a low grade of polysomy (three to five copies) of chromosome 7. Polysomy was more frequently observed in DIC (25%; $P = 0.001$). We tried to correlate polysomy of *MET* in the DIC group with grade, tumor size, lymph node status, clinical stage and expression of HER2, P53, estrogen receptor (ER) and progesterone receptor (PR). We observed that the absence of expression of PR was the unique statistically significant variable ($P = 0.001$). Moreover, the ER+/PR- samples presented the highest rate of polysomy (38%) compared to ER+/PR+ tumors (15%) (Table 1).

Out of 168 tumors analyzed by immunohistochemistry, 65 (38.7%) presented expression of c-Met. When histological types were compared, the DIC group also showed the highest number of c-Met-positive samples (48%; $P = 0.001$). From the analysis with the clinico-pathological variables, the negativity for PR was again statistically significant ($P = 0.001$). The ER+/PR- tumors presented more frequent expression of c-Met (68%) compared to ER+/PR+ tumors (32%) and were correlated with polysomy ($P = 0.020$) (Table 2).

We can conclude that amplification of *MET* in breast cancer is not a common event, as opposed to other cancer subtypes (renal, gastric and lung carcinomas). Although found in breast tumors, it seems that overexpression of c-Met is not mainly due to increassed gene copy number of *MET*/polysomy7. However, polysomy in the ER+/PR- group could be an

DIC = ductal infiltrating carcinoma; ER = estrogen receptor; FISH = fluorescent *in situ* hybridization; PR = progesterone receptor.

**Table 1**

**Results of IHC of c-Met and FISH of LSI D7S486/CEP7 applied to lobular and ductal carcinomas**

| | IHC c-Met | | FISH *MET* | | FISH + IHC |
|---|---|---|---|---|---|
| | Negative | Positive | Negative | Polysomy | PE + P |
| Carcinoma type | | | | | |
| Lobular | 57 (76%) | 18 (24%) | 61 (81%) | 15 (19%) | 5 (7%) |
| Ductal (DIC) | 42 (52%) | **38 (48%)** | 60 (75%) | **20 (25%)** | **13 (16%)** |
| DIC type | | | | | |
| ER+/PR+ | 31 (68%) | 15 (32%) | 39 (85%) | 7 (15%) | 3 (6%) |
| ER+/PR- | 11 (32%) | **23 (68%)** | 21 (62%) | **13 (38%)** | **10 (29%)** |

DIC, ductal infiltrating carcinoma; PE, positive expression; ER, estrogen receptor; FISH, fluorescent *in situ* hybridization; IHC, immunohistochemistry; P, polysomy; PR, progesterone receptor. In bold we remark the positive FISH and IHQ results for DIC as well as for ER+/PR- tumors

**Table 2**

**IHC and FISH results of *MET* according to the status of PR receptor in DIC carcinomas**

| | ER+/PR+ (n= 46) | | ER+/PR- (n = 34) | |
|---|---|---|---|---|
| FISH *MET* | IHC Negative | IHC Positive | IHC Negative | IHC Positive |
| FISH Negative | 27 (59%) | 12 (26%) | 9 (23%) | 13 (38%) |
| FISH Polysomy | 4 (9%) | **3 (6%)** | 3 (9%) | **10 (29%)** |

DIC, ductal infiltrating carcinoma; ER, estrogen receptor; FISH, fluorescent *in situ* hybridization; IHC, immunohistochemistry; P, polysomy; PR, progesterone receptor. In bold we remark the FISH and IHQ positive results to compare both groups.

important mechanism - although not the only one - responsible for the differential expression observed in this type of DIC. This c-Met overexpression and the presence of polysomy 7 could be important events to be considered with regard to the known poor response to endocrine therapies of ER+/PR- breast tumors. Lack of PR expression in ER+ tumors may be a surrogate marker of aberrant growth factor signaling [3] that could be associated with their more aggressive outcome, as has already been described [4].

Our study suggests that it would be interesting to investigate new therapeutic options for ER+/PR- DIC, which may include c-Met inhibitors.

## Competing interests

The authors declare that they have no competing interests.

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