Phosphorylated protein phosphatase 2A determines poor outcome in patients with metastatic colorectal cancer

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Background: Protein phosphatase 2A (PP2A) is a tumour suppressor frequently inactivated in human cancer and its tyrosine-307 phosphorylation has been reported as a molecular inhibitory mechanism.

Methods: Expression of phosphorylated PP2A (p-PP2A) was evaluated in 250 metastatic colorectal cancer (CRC) patients. Chi-square, Kaplan–Meier and Cox analyses were used to determine correlations with clinical and molecular parameters and impact on clinical outcomes.

Results: High p-PP2A levels were found in 17.2% cases and were associated with ECOG performance status (P=0.001) and presence of synchronous metastasis at diagnosis (P=0.035). This subgroup showed substantially worse overall survival (OS) (median OS, 6.0 vs 26.2 months, P<0.001) and progression-free survival (PFS) (median PFS, 3.8 vs 13.3 months, P<0.001). The prognostic impact of p-PP2A was particularly evident in patients aged <70 years (P<0.001). Multivariate analysis revealed that p-PP2A retained its prognostic impact for OS (hazard ratio 2.7; 95% confidence interval, 1.8–4.1; P<0.001) and PFS (hazard ratio 3.0; 95% confidence interval, 1.8–5.0; P<0.001).

Conclusions: Phosphorylated PP2A is an alteration that determines poor outcome in metastatic CRC and represents a novel potential therapeutic target in this disease, thus enabling to define a subgroup of patients who could benefit from future treatments based on PP2A activators.

Colorectal cancer (CRC) is the most common gastrointestinal cancer and its aetiology involves an interaction of genetic and epigenetic alterations with environmental factors such as diet components that contribute to cancer development. A correct balance between kinase and phosphatase activities is essential in maintaining cell homeostasis (Hunter, 1995). The presence of alterations affecting kinase activities has been shown to be recurrent in many cancers, and therapies based on kinase inhibitors have been developed in the previous years. Although the role of phosphatases remains underexplored in comparison, it is true that phosphatases like protein phosphatase 2A (PP2A) have progressively been considered as potential tumour suppressors.

Protein phosphatase 2A is a major serine/threonine phosphatase that consists of a heterotrimer that includes a catalytic, a scaffold, and a regulatory subunit involved in the specificity and localisation of the holoenzyme. Owing to the multiple existing isoforms and splicing variants for each PP2A subunit, especially in the case of the regulatory subunit, PP2A can form a wide variety of heterotrimeric complexes with distinct substrate specificities and they therefore have different biological functions (Arino et al, 1988; Zhou et al, 2003; Eichhorn et al, 2009). Of importance, PP2A plays a pivotal role in regulating many signalling pathways (Millward et al, 1999; Janssens and Goris, 2001; Janssens et al, 2005; Mumbly, 2007) and its inactivation has been described as a common event in...
the cancerous cell through several molecular strategies (Mumbry, 2007; Westermarck and Hahn, 2008; Eichhorn et al, 2009).

Interestingly, Chen et al (1992) demonstrated that in vitro phosphorylation of PP2A at Y307 by protein tyrosine kinases led to its inactivation. Moreover, phosphorylation of PP2A at Y307 has been described as a molecular PP2A-inactivating mechanism with relevance in chronic and acute leukemias or Alzheimer’s disease (Perrotti and Neviani, 2008; Cristobal et al, 2010, 2011; Xiong et al, 2013). Although PP2A has been proposed as a novel therapeutic target in several tumours (Perrotti and Neviani, 2008, 2013; Kaley and Sablina, 2011; Voronkov et al, 2011), the potential relevance of PP2A as a druggable tumour suppressor in CRC still needs to be clarified. However, several observations indicate that PP2A inhibition could be playing an important role in CRC development. Thus, the presence of reported PP2A-inactivating mutations affecting the scaffold PP2A subunit in CRC (Wang et al, 1998; Takagi et al, 2000; Ruediger et al, 2001; Tamaki et al, 2004), together with the fact that PP2A seems to modulate the sensitivity of CRC cells to different treatments (Tan et al, 2010; Kumar et al, 2012; Lin et al, 2012), prompted us to hypothesise that PP2A could represent a novel molecular target with relevance in CRC.

In this report, we studied p-PP2A in a cohort of 250 metastatic CRC patients, observing that high p-PP2A levels were associated with worse ECOG performance status and the presence of synchronous metastasis. Of importance, the high p-PP2A subgroup showed a markedly shorter overall survival (OS) and progression-free survival (PFS), with significance in both wild-type and mutated KRAS subgroups. Interestingly, multivariate analysis showed that p-PP2A has an independent prognostic value for OS and PFS in metastatic CRC.

RESULTS

Prevalence of p-PP2A in metastatic CRC and its association with clinical and molecular parameters. To study the prevalence of p-PP2A and its potential clinical significance in CRC, we quantified the expression of p-PP2A by immunohistochemistry in a series of 250 patients with metastatic CRC, correlated the results obtained with clinical and molecular features, and studied the prognostic relevance of this aberration. Patient characteristics are presented in Supplementary Table 1. High p-PP2A expression was observed in 17.2% cases (43 out of 250). The prevalence of PP2A hyperphosphorylation was higher in women than in men (24.5% vs 12.8%, \(P = 0.018\)). Moreover, we found high p-PP2A to be associated with worse ECOG performance status (35.7% vs 15.5%, \(P = 0.001\)), and with the presence of synchronous metastasis (20.9% vs 11.3%, \(P = 0.035\)). Association between p-PP2A and clinical and genetic parameters is shown in Table 1.
Clinical significance of p-PP2A in metastatic CRC. Clinical follow-up data were available for 243 cases, 149 men and 94 women, with a median age of 69.5 years (age range: 29–92). Median OS of the global cohort was 21.9 months (95% confidence interval, 17.2–26.6 months). We found that the subgroup of patients with high p-PP2A showed a substantially shorter OS (median OS, 6.0 vs 26.2 months, P<0.001) (Figure 1A) and PFS (median PFS, 3.8 vs 13.3 months, P<0.001) (Figure 1B). Interestingly, the prognostic impact of p-PP2A was particularly evident in the subgroup of patients aged <70 years (median OS, 6.2 vs 33.2 months, P<0.001; median PFS, 4.4 vs 16.4 months, P<0.001); however, significance was also achieved in the subgroup of elderly patients (median OS, 5.9 vs 15.2 months, P=0.012; median PFS, 3.8 vs 7.6 months, P=0.020) (Figure 2). To further investigate the

Table 1. Association between p-PP2A and clinical and genetic parameters in 250 patients with metastatic CRC

|                      | No. of cases | No. p-PP2A − (%) | No. p-PP2A + (%) | P      |
|----------------------|--------------|------------------|------------------|--------|
| p-PP2A               | 250          | 207 (82.8)       | 43 (17.2)        |        |
| Sex                  |              |                  |                  | 0.018  |
| Male                 | 156          | 136 (87.2)       | 20 (12.8)        |        |
| Female               | 94           | 71 (75.5)        | 23 (24.5)        |        |
| Age                  |              |                  |                  | 0.306  |
| <70                  | 116          | 98 (84.5)        | 18 (15.5)        |        |
| ≥70                  | 116          | 92 (79.3)        | 24 (20.7)        |        |
| ECOG                 | 224          | 184              | 40               | 0.001  |
| 0–2                  | 182          | 157 (84.5)       | 25 (15.5)        |        |
| 3–4                  | 42           | 27 (64.3)        | 15 (35.7)        |        |
| Site of primary tumour|             |                  |                  | 0.552  |
| Cecum                | 24           | 17 (84.5)        | 7 (15.5)         |        |
| Right colon          | 37           | 31 (79.3)        | 6 (20.7)         |        |
| Transverse colon     | 10           | 7 (70)           | 3 (30)           |        |
| Left colon           | 21           | 18 (85.7)        | 3 (14.3)         |        |
| Sigma                | 73           | 61 (83.6)        | 12 (16.4)        |        |
| Rectum               | 85           | 73 (85.9)        | 12 (14.1)        |        |
| Synchronous metastasis|            |                  |                  | 0.035  |
| No                   | 85           | 76 (89.4)        | 9 (10.6)         |        |
| Yes                  | 159          | 125 (78.6)       | 34 (21.4)        |        |
| Number of metastatic sites | |                  |                  | 0.620  |
| 1–2                  | 226          | 188 (83.2)       | 38 (16.8)        |        |
| >2                   | 24           | 19 (79.2)        | 5 (20.8)         |        |
| Liver metastasis     | 244          | 201              | 43               | 0.294  |
| No                   | 79           | 68 (86.1)        | 11 (13.9)        |        |
| Yes                  | 165          | 133 (80.6)       | 32 (19.4)        |        |
| Lung metastasis      | 244          | 201              | 43               | 0.323  |
| No                   | 166          | 134 (80.7)       | 32 (19.3)        |        |
| Yes                  | 78           | 67 (85.9)        | 11 (14.1)        |        |
| Peritoneal metastasis| 244          | 201              | 43               | 0.846  |
| No                   | 196          | 161 (82.1)       | 35 (17.9)        |        |
| Yes                  | 48           | 40 (83.3)        | 8 (16.7)         |        |
| MSI                  | 240          | 189              | 41               | 0.774  |
| No                   | 226          | 187 (82.7)       | 39 (17.3)        |        |
| Yes                  | 14           | 12 (85.7)        | 2 (14.3)         |        |
| KRAS mutations       | 246          | 203              | 43               | 0.873  |
| No                   | 140          | 116 (82.9)       | 24 (17.1)        |        |
| Yes                  | 106          | 87 (72.1)        | 33 (27.9)        |        |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; MSI = magnetic source imaging; p-PP2A = protein phosphatase 2A. P values in bold font indicate differences statistically significant.
Figure 1. Clinical significance of p-PP2A in metastatic CRC: (A) Immunohistochemical detection of p-PP2A showing positive and negative staining. The line shows 25 μm. Magnification × 400; Kaplan–Meier analyses of overall survival (B) and progression-free survival (C) in a cohort of 243 patients with metastatic CRC.

Figure 2. Kaplan–Meier analyses in the subgroups of patients aged < and ≥70 years: (A) Overall survival; (B) progression-free survival.
clinical relevance of p-PP2A in metastatic CRC we analysed its potential prognostic value by stratifying our cohort based on KRAS mutation status, and we found that p-PP2A retained its prognostic impact in both KRAS wild-type and KRAS mutated subgroups with a similar significance (Supplementary Figure 3). Importantly, multivariate analysis demonstrated that p-PP2A is an unfavourable independent factor associated with OS (hazard ratio 2.7; 95% confidence interval, 1.8–4.1; \( P < 0.001 \)) (Table 2) and PFS (hazard ratio 3.0; 95% confidence interval, 1.8–5.0; \( P < 0.001 \)) (Table 3) in metastatic CRC.

**DISCUSSION**

We report here that PP2A hyperphosphorylation is a recurrent molecular event in metastatic CRC associated with worse ECOG performance status and the presence of synchronous metastasis. Importantly, this alteration determines a markedly shorter overall and PFS, especially in the subgroup of patients younger than 70 years. The prognostic impact was similar in the KRAS wild-type and mutated subgroups. Moreover, multivariate analysis showed that high p-PP2A expression has an independent prognostic value for OS and PFS in patients with metastatic CRC. Of importance, our data provide strong evidence that p-PP2A has a potential prognostic value and could be a promising therapeutic target for future clinical trials using PP2A activators.

Despite progressive advances in our understanding of the molecular biology of CRC, patient outcomes in the metastatic subgroup are still very poor. Therefore, it is necessary to develop alternative therapeutic strategies to improve the survival of these patients. The tumour suppressor PP2A has been shown to be functionally inactivated in several types of human cancer through different contributing mechanisms, including the hyperphosphorylation of its catalytic subunit (Saydam et al., 2003; Cristobal et al., 2011). However, in comparison with other tumour models, the relevance of the tumour suppressor role of PP2A and its potential clinical significance in CRC remains mostly unknown. Therefore, to evaluate the clinical relevance of PP2A phosphorylation in metastatic CRC, we analysed the expression of p-PP2A in a cohort of 250 patients with metastatic CRC, observing high p-PP2A in 17.2% of cases (Table 1). The prevalence observed for this alteration in our cohort suggests that this would be a relevant molecular mechanism to inactivate PP2A in CRC.

Moreover, we observed that high p-PP2A correlated positively with a high grade of ECOG performance status and with the existence of synchronous metastasis at diagnosis in our cohort (Table 1). These results prompted us to hypothesise that this could be a molecular alteration characteristic of the advanced stages of CRC that could therefore have a prognostic value in patients with metastatic disease. In concordance with this, we observed that the subgroup of patients with high p-PP2A showed a substantially shorter OS and PFS compared with the low-p-PP2A subgroup (Figure 1), confirming the clinical relevance of p-PP2A in metastatic CRC. Moreover, the fact that the prognostic impact of p-PP2A showed higher significance in the subgroup of patients aged <70 years (Figure 2) is very interesting since this subgroup includes cases with more options from a therapeutic perspective that could benefit from the treatment with PP2A activating drugs.

| Table 2. Univariate and multivariate Cox analyses in the cohort of 243 patients with mCRC |
| --- |
| **Univariate OS analysis** | **Multivariate OS Cox analysis** |
| HR | 95% CI | Significance | HR | 95% CI | Significance |
| --- | --- | --- | --- | --- | --- |
| Age | | | 1.000 | | <0.001 |
| 1.000 | | | 1.000 | | 0.249 |
| Gender | | | 1.875 | 1.352–2.599 | | 1.250 | 0.855–1.827 |
| Male | | | 0.311 | | — |
| Female | | | 0.848 | 0.616–1.167 | | — | — |
| Synchronous | | | 0.118 | | — |
| No | | | 1.301 | 0.935–1.811 | | — | — |
| Yes | | | | | | | |
| ECOG | | | <0.001 | | <0.001 |
| 0–1 | 1.000 | | 1.000 | | |
| 2–3 | 1.925 | 1.588–2.333 | | 1.777 | 1.427–2.213 |
| MSI | | | 0.450 | | — |
| No | | | 1.000 | | — |
| Yes | | | 1.281 | 0.674–2.437 | | — | — |
| Number of metastatic sites | | | 0.076 | | — |
| 1–2 | 1.000 | | — | — |
| >2 | 1.250 | 0.977–1.600 | | — | — |
| p-PP2A | | | <0.001 | | <0.001 |
| No | | | 1.000 | | — |
| Yes | | | 2.838 | 1.935–4.164 | | 2.743 | 1.819–4.138 |

**Abbreviations:** CI = confidence interval; HR = hazard ratio; OS = overall survival; MSI = magnetic source imaging; p-PP2A = protein phosphatase 2A. P values in bold font indicate differences statistically significant.
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Table 3. Univariate and multivariate Cox analyses in the cohort of 243 patients with mCRC

| | Univariate PFS analysis | | Multivariate PFS Cox analysis |
|---|---|---|---|
| | HR | 95% CI | Significance | HR | 95% CI | Significance |
| Age | | | | | | |
| | 1.000 | | | 1.000 | | |
| | 1.966 | 1.318–2.932 | 0.001 | 1.476 | 0.933–2.333 | 0.096 |
| Gender | | | | | | |
| Male | 1.000 | | | | | |
| Female | 0.897 | 0.601–1.339 | 0.595 | | | |
| Synchronous | | | | | | |
| No | 1.000 | | | | | |
| Yes | 1.522 | 0.990–2.341 | 0.056 | | | |
| ECOG | | | | | | |
| 0–1 | 1.000 | | | 1.000 | | |
| 2–3 | 1.556 | 1.224–1.978 | | 1.420 | 1.081–1.866 | 0.012 |
| MSI | | | | | | |
| No | 1.000 | | | | | |
| Yes | 1.445 | 0.584–3.577 | 0.426 | | | |
| Number of metastatic sites | | | | | | |
| 1–2 | 1.000 | | | 1.000 | | |
| >2 | 1.374 | 1.033–1.827 | | 1.564 | 1.165–2.099 | |
| p-PP2A | | | | | | |
| No | 1.000 | | | 1.000 | | |
| Yes | 3.046 | 1.885–4.822 | | 3.008 | 1.804–5.016 | <0.001 |

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; MSI = magnetic source imaging; PFS = progression-free survival; p-PP2A = protein phosphatase 2A. P values in bold font indicate differences statistically significant.

In conclusion, we show that p-PP2A is a common alteration with clinical significance in metastatic CRC. Of importance, p-PP2A could serve as a novel molecular target that can help define a subgroup of metastatic CRC patients with worse outcome that could benefit by the future incorporation of PP2A-activating drugs in anticancer protocols.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Arino J, Woon CW, Brautigan DL, Miller Jr TB, Johnson GL (1988) Human liver phosphatase 2A: cDNA and amino acid sequence of two catalytic subunit isotypes. *Proc Natl Acad Sci USA* 85(12): 4252–4256.
Bhardwaj A, Singh S, Srivastava SK, Arora S, Hyde SJ, Andrews J, Grizzle WE, Singh AP (2014) Restoration of PPP2CA expression...
reverses epithelial-to-mesenchymal transition and suppresses prostate tumour growth and metastasis in an orthotopic mouse model. Br J Cancer 110(8): 2000–2010.

Chen J, Martin BL, Brautigan DL (1992) Regulation of protein serine-threonine phosphatase type 2A by tyrosine phosphorylation. Science 257(5074): 1261–1264.

Cristobal I, Blanco FJ, Garcia-Ortiz L, Marcotegui N, Vicente C, Rifen J, Novo FJ, Bandres E, Calasanz MJ, Bernabeu C, Odero MD (2010) SETBP1 overexpression is a novel leukaemogenic mechanism that predicts adverse outcome in elderly patients with acute myeloid leukemia. Blood 115(3): 615–625.

Cristobal I, Garcia-Ortiz L, Cirauqui C, Alonso MM, Calasanz MJ, Odero MD (2011) PP2A impaired activity is a common event in acute myeloid leukemia and its activation by forskolin has a potent anti-leukemic effect. Leukemia 25(4): 606–614.

Cristobal I, Manso R, Rincón R, Caramés C, Senin C, Borrero A, Martínez-Users J, Rodríguez M, Zazo S, Aguilera O, Madoz-Gúrpide J, Rojo F, García-Fonciellas J (2014) PP2A inhibition is a common event in colorectal cancer and its restoration using FTY720 shows promising therapeutic potential. Mol Cancer Ther 13(4): 938–947.

Eichhorn PJ, Creighton MP, Bernards R (2009) Protein phosphatase 2A regulatory subunits and cancer. Biochim Biophys Acta 1795(1): 1–15.

Generali D, Buffa FM, Berruti A, Brizzi MP, Campo L, Bonardi S, Bersiga A, Allevi G, Milani M, Aguggini S, Papotti M, Dogliotti L, Bottini A, Harris AL, Fox SB (2009) Phosphorylated ERalpha, HIF-1alpha, and MAPK signaling as predictors of primary endocrine treatment response and 470 resistance in patients with breast cancer. J Clin Oncol 27(2): 227–234.

Hunter T (1995) Protein kinases and phosphatases: the yin and yang of protein phosphorylation and signalling. Cell 80(2): 223–236.

Janssens V, Goris J (2001) Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. Biochem J 353(Pt3): 417–439.

Janssens V, Goris J, Van Hoof C (2005) PP2A: the expected tumor suppressor. Curr Opin Genet Dev 15(1): 34–41.

Kalev P, Sabliina AA (2011) Protein phosphatase 2A as a potential target for anticancer therapy. Anticancer Agents Med Chem 11(1): 38–46.

Kumar A, Pandurangan AK, Lu F, Fyrst H, Zhang M, Byun HS, Bittman R, Saha JD (2012) Chemopreventive sphinogdisin downregulate Wnt signaling via a PP2A/AKI/GSK3β pathway in colon cancer. Carcinogenesis 33(9): 1726–1735.

Lin SP, Lee YT, Yang SH, Miller SA, Chiou SH, Hung MC, Hung SC (2012) Colon cancer stem cells resist antiangiogenesis therapy-induced apoptosis. Cancer Lett 328(2): 226–234.

McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics (2005) Reporting recommendations for tumor marker prognostic studies. J Clin Oncol 23(36): 9067–9072.

Millward TA, Zolnierowicz S, Hemmings BA (1999) Regulation of protein kinase cascades by protein phosphatase 2A. Trends Biochem Sci 24(5): 186–191.

Mumby M (2007) PP2A: unveiling a reluctant tumor suppressor. Cell 130(1): 21–24.

Perrotti D, Neviani P (2008) Protein phosphatase 2A (PP2A), a drugable tumor suppressor in Ph1 (+) leukemias. Cancer Metastasis Rev 27(2): 159–168.

Perrotti D, Neviani P (2013) Protein phosphatase 2A: a target for anticancer therapy. Lancet Oncol 14(6): e229–e238.

Rosa R, Marciano R, Malapelle U, Formisano L, Nappi L, D’Amato C, D’Amato V, Damianio V, Marile G, Del Vecchio S, Zanetti A, Greco A, De Stefano A, Carlomagno C, Veneziani BM, Tronocone G, De Placido S, Bianco R (2013) Sphingosine kinase 1 overexpression contributes to cetzumab resistance in human colorectal cancer models. Clin Cancer Res 19(1): 138–147.

Ruediger R, Pham HT, Walter G (2001) Alterations in protein phosphatase 2A subunit interaction in human carcinomas of the lung and colon with mutations in the A beta subunit gene. Oncogene 20(15): 1892–1899.

Saydam G, Aydin HH, Sahin F, Selvi N, Oktem G, Terzioglu E, Buyukkececi F, Onay SB (2003) Involvement of protein phosphatase 2A in interferon-alpha-2b-induced apoptosis in K562 human chronic myelogenous leukaemia cells. Leuk Res 27(8): 709–717.

Takagi Y, Futamura M, Yamaguchi K, Aoki S, Takahashi T, Saji S (2000) Alterations of the PPP2R1B gene located at 11q23 in human colorectal cancers. Gut 47(2): 268–271.

Tamaiki M, Goi T, Hirono Y, Katayama K, Yamaguchi A (2004) PPP2R1B gene alterations inhibit interaction of PP2A-Abeta and PP2A-C proteins in colorectal cancers. Oncol Rep 11(3): 655–659.

Tan J, Lee PL, Li Z, Jiang X, Lim YC, Hooi SC, Yu Q (2010) B55α-associated PP2A complex controls PDK1-directed myc signaling and modulates rapamycin sensitivity in colorectal cancer. Cancer Cell 18(5): 459–471.

Voronkov M, Braithwaite SP, Stock JB (2011) Phosphoprotein phosphatase 2A: a novel druggable target for Alzheimer’s disease. Future Med Chem 3(7): 821–833.

Wang SS, Esplin ED, Li JL, Huang L, Gazdar A, Minna J, Evans GA (1998) Alterations of the PPP2R1B gene in human lung and colon cancer. Science 282(5387): 284–287.

Westermarck J, Halm WC (2008) Multiple pathways regulated by the tumor suppressor PP2A in transformation. Trends Mol Med 14(4): 152–160.

Xiong Y, Jing XP, Zhou WX, Wang XL, Yang Y, Sun XY, Qiu M, Cao FY, Lu YM, Liu R, Wang JZ (2013) Zinc induces protein phosphatase 2A inactivation and tau hyperphosphorylation through Src dependent PP2A (tyrosine 307) phosphorylation. Neurobiol Aging 34(3): 745–756.

Zhou J, Pham HT, Ruediger R, Walter G (2003) Characterization of the Aalpha and Abeta subunit isoforms of protein phosphatase 2A: differences in expression, subunit interaction, and evolution. Biochem J 369(Pt2): 387–398.

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