



Commentary

PP2A Level in Colorectal Cancer Cells Predicts the Response of p38 Targeted Therapy



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The p38 mitogen-activated protein kinases (MAPK) play an important role in the regulation of cell proliferation and survival, in response to various environmental cues, e.g., oxidative stress and inflammatory cytokines (Cuenda and Rousseau, 2007). p38 MAPK activity is elevated in types of cancer, including colorectal cancer (CRC) (Gupta et al., 2014), and accordingly, several p38 inhibitors (p38is) have been in early clinical trials. However, surprisingly, none of the p38is has shown positive effects on CRC. This remains mysterious.

In this issue of *EBioMedicine*, Zhang et al. (2015), for the first time, reported opposite responses of two subgroups of CRC cells to p38is. In the first subgroup (including RKO, CACO2 and SW480), named p38i-inhibited group, p38 inhibitor (p38i) SB202190 inhibited cell proliferation and induced apoptosis; while in the second subgroup (including HCT116, SW1116 and SW620), designated p38i-stimulated group, SB202190 increased cell proliferation and survival. Similar results were observed in LY2228820 and BIRB796, two other p38is. The findings were verified in CRC xenografts in mice, indicating that there exist two subgroups of CRC cells, which respond to p38is differentially.

Interestingly, Zhang et al. (2015) also found opposing effects of p38is on mTORC1 in the two subgroups of CRC cells, correlating with the effects on cell growth. Since SB202190 inhibits mTORC1 through MAPK-activated protein kinase 2 (MK2)-dependent phosphorylation of TSC2 (S1254) (Li et al., 2003), and MK2 is directly regulated by p38 MAPK (Cuenda and Rousseau, 2007). Zhang et al. (2015) hypothesized that the opposite effects of p38is on mTORC1 in the CRC cells link to the status of TSC1/2 complex, a negative regulator of mTORC1 (Inoki et al., 2002). The results support their hypothesis, as silencing TSC1 or TSC2 abrogated the negative or positive effects of SB202190 on mTORC1 and cell growth.

TSC2 can be phosphorylated by Akt at T1462, p38/MK2 at S1254, and ERK-RSK at S664/S1798 (Inoki et al., 2002; Li et al., 2003; Roux et al., 2004; Ma et al., 2005). Zhang et al. (2015) also found that TSC2 phosphorylation differed between the two subgroups of CRC cells, in response to p38i. In the p38i-inhibited group, SB202190 suppressed p38/MK2-mediated TSC2 phosphorylation (S1254), causing activation of TSC1/2 and thereby inhibition of mTORC1, but had no effects on Akt/ERK-RSK-mediated TSC2 phosphorylations. In contrast, in the

p38i-stimulated group, SB202190 enhanced ERK/RSK-mediated TSC2 phosphorylation (S664 and S1798), leading to inhibition of TSC1/2 and activation of mTORC1. Similarly, Akt or p38/MK2-mediated TSC2 phosphorylations were not influenced by SB202190. Hence, the results suggest that p38/MK2 and ERK/RSK mediate the opposing effects of p38i on mTORC1 via regulating different phosphorylation sites of TSC2 in the two subgroups.

Protein phosphatase 2A (PP2A), a serine–threonine phosphatase, consists of the structural A subunit, regulatory B subunit, and catalytic C subunit (Seshacharyulu et al., 2013). It has been described that p38 MAPK negatively regulates ERK in a PP2A-dependent manner in rat cardiac ventricular myocytes (Liu and Hofmann, 2004). Likely, the differential effects of p38i on TSC phosphorylation are related to PP2AC levels in the two subgroups of CRC cells. To this end, Zhang et al. (2015) examined PP2AC expression in the cells. They found that PP2AC was expressing at a much lower level in p38i-inhibited group than in p38i-stimulated group, limiting the negative regulation of p38 on ERK. Silencing PP2AC in the p38i-stimulated CRC cells diminished the activation effect of SB202190 on mTORC1, and reprogrammed the selective response of TSC2 phosphorylation to the p38i from p38-ERK-RSK-TSC2 to p38-MK2-TSC2. On the contrary, overexpressing PP2AC in the p38i-inhibited CRC cells reduced the inhibitory effect of SB202190 on mTORC1, and reprogrammed the selective response of TSC2 phosphorylation to the p38i from p38-MK2-TSC2 to p38-ERK-RSK-TSC2. Thus, the data support the notion that PP2AC level in CRC cells determines their differential responses to p38i.

To demonstrate whether the level of PP2AC expression in CRC can be used as a biomarker for treatment, patient-derived xenograft (PDX) mouse models were employed (Zhang et al., 2015). They found that human CRC tumors expressing low levels of PP2AC showed good response to SB202190, whereas human CRC tumors expressing high levels of PP2AC displayed poor or adverse response to SB202190. Thus, the results suggest that PP2AC expression level may serve as a useful biomarker for p38 targeted therapy.

Since p38i activation of mTORC1 correlates with the resistance in p38i-stimulated subgroup, Zhang et al. (2015) also tested whether mTOR kinase inhibitors were able to overcome the resistance of CRC cells to p38i. They found that SB202190 alone stimulated SW620 xenograft growth, and mTOR kinase inhibitor OSI-027 alone did not inhibit SW620 tumor growth. When combined, the two drugs remarkably inhibited the tumor growth and induced apoptosis of SW620 cells.

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This study is a good example to show the necessity and importance of combinational chemotherapy.

In summary, the findings from Zhang et al. (2015) shed new light on targeted chemotherapy and combinational chemotherapy. The intrinsic properties of different tumor cells may render differential responses to the same treatment. Hence, identifying the heterogeneity within one tumor type is crucial for personalized treatment. Undoubtedly, more efforts are needed to validate whether PP2AC expression level can serve as a biomarker for p38 targeted therapy. Also, it would be interesting to study whether PP2AC level is also a major determinant for other cancers (e.g., lung, breast or prostate cancer) to respond to p38 targeted therapy. The finding of opposing effects of p38 on two subgroups of CRC cells gives us warning in proper categorization of patients to avoid promoting tumor growth through chemotherapies.

Disclosures

The authors declare no conflicts of interest.

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