Editorial

MYCing and YAPing the escape of tumor cell growth arrest after chronic PI3K/mTOR inhibition

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The phosphatidylinositol-3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) signaling cascades represent two critical and highly interconnected pathways regulating cellular proliferation, metabolism, differentiation and survival—particularly in response to cytotoxic stress (1). As a single pathway exploited by multiple neoplasms, mutations of PI3K/mTOR's components represent attractive pharmacological targets, leading to the development of a wide array of targeted therapies (2).

In the past decade, research into the field of mTOR inhibitors has led to the development of several clinical trials of different pharmacological agents targeting a diverse range of nodes along the molecular machinery of the pathway. Much as any other anti-cancer therapy, a frequent issue that is seen is either the pre-existence or the eventual development of drug resistance of the neoplastic cells to the treatment. In the case of PI3K/mTOR's in particular, there are several identified mechanisms conferring chemoresistance, the most prominent of which is receptor tyrosine kinase (RTK) up-regulation (3).

In the study of Muranen *et al.*, PI3K/mTOR inhibition was shown to be overcome by a compensatory up-regulation of MYC and YAP1; this novel chemoresistance mechanism was shown to be context-dependent and regulated through a bivalent relationship between the ERK and p38 MAPK pathways. The authors proposed a pathophysiological model in which the chronic PI3K/mTOR inhibition induced a state of tumor dormancy, firmly dependent on the ERK/p38 switch that eventually leads to tumor regrowth (4).

Among the most salient mechanisms of chemoresistance, parallel cross-talking pathways that compensate the suppression of PI3K/mTOR have been identified as potential culprits. In this manner, while Ras-ERK is often recruited along the mTOR pathway along the course of tumorigenesis, single targeting of mTOR leads to diminished cytotoxic effects. The multilevel cross-activation of PI3K/mTOR by RAS-ERK guarantees that several nodes along their common cascades (such as mTORC1) can be recruited by oncogenic mutations and facilitate an escape from cytostasis. As a means to overcome this hurdle, dual targeting ERK and mTOR has been proven to be an effective strategy at least in both cellular and animal models of cancer (5). The study of Muranen *et al.* outlines the importance of this mechanism; the authors conclude however, that the sole activation of the RAS-ERK pathway would not be enough to allow neoplastic cells a reprieve from PI3K/mTOR mediated cytostasis (4).

An apparent comparison between the literature and the conclusion of the authors would be that of a conflict; it is however possible to consider both observations in a common pathophysiological context, should the relevant molecular events be placed in a timeline. Therefore, a putative model of tumorigenesis would require the assumption that PI3K/mTOR and RAS-ERK oncogenic deregulations co-exist

initially; single target therapies are effective, until the point where a biological adaptation (i.e., isoform switching) occurs, and the un-inhibited pathway cross-activates components of the inhibited one. Corresponding to the observations present in the literature, dual inhibitions would be apparently effective, even achieving cytotoxicity. Finally, the treatment-induced noxious milieu would trigger a p38 homeostatic up-regulation, thus alleviating the cytotoxic burden in favor of neoplastic cell survival (6). At this point, the pathophysiological model proposed by Muranen *et al.* would become highly relevant.

It is important to point out that the proposed p38/ERK switch is not only intrinsic to neoplastic processes, but also to normal cell growth and proliferation under the influence of the appropriate upstream signal (7). It would thus be critical to determine whether other, cell-specific upstream targets could produce a particular signature of a perturbed p38/ERK, in the setting of neoplasia. Provided that in a physiological setting, different upstream effectors of this switch mediate specific signal transduction cascades, the therapeutics of dual PI3K/mTOR and RAS-ERK inhibition would be even more specialized into delivering an agent towards the most effective, per neoplasm, p38/ERK interactor.

In the context described by a p38/ERK switch set to favor proliferation, Muranen *et al.* further identified the interplay between c-MYC and Yes Associated Protein 1 (YAP1) as the main mechanism conferring chemoresistance in neoplastic cells under chronic PI3K/mTOR suppression (4). The interaction between c-MYC and YAP1 in liver cancer has been reported as yet another molecular switch, promoting tumorigenesis in a complimentary manner (8). In a recent report, Zhang *et al.* describe and expand on this interaction by introducing the signaling of YAP/p21/c-Myc/Bcl-xL in osteosarcoma. In their study, the bromodomain inhibitor JQ1 exerts its pro-apoptotic activity through the aforementioned expanded c-MYC/YAP axis (9). Interestingly, JQ1, a small molecule inhibitor of BRD4, has been shown to target the PI3K/mTOR in PTEN-positive endometrial cancers (10). Pertinent to the above is the critical observation that the recruitment of the MYC/YAP axis in the tumorigenic process appears to be pleiotropic when examining different animal cancer models or data derived from human patients. Indicatively, a MYC/YAP/TAZ interaction in mammary epithelial cells has been shown to favor high cellular consumption, with a concurrent implication for mitochondrial dynamics (11).

A final piece of the puzzle would be provided by the YAP/cyclic adenosine monophosphate response element-binding protein (CREB) interaction, as seen in hepatic cancer (12). While CREB up-regulates YAP expression, YAP stabilizes CREB and eventually ushers the molecule for degradation. This final step is catalyzed by p38-mediated phosphorylation of a critical threonine residue; YAP however functions as a limiting factor to this final interaction, closing the full feedback loop (12). Consistent with the literature mentioned above, Muranen *et al.* describe a similar dependency between CREB and YAP in their own model.

Summarizing our Editorial on the study of Muranen *et al.*, we would have to acknowledge that loosely connected pieces of the literature regarding PI3K/mTOR inhibitor resistance come together in a single study, stemming from the same experimental rationale. Further denoting the importance of their work is the existence of molecules such as JQ1, fitting already into their putative model; possibly, this will commence yet another venue of future research into this very interesting mechanism of chemoresistance.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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