Detecting Specific Drug Responses

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Traditional anticancer therapy involves treatment with radiation and DNA-damaging chemotherapies. More recently, insight into the molecular and genetic changes associated with cancer has led to a shift in anticancer drug development and new drugs typically modulate specific molecular targets associated with onset and progression of the disease. The oncologist’s armamentarium has thus expanded substantially, and anticancer therapy is becoming increasingly personalized. However, assessing response to treatment can be challenging. Response to traditional chemotherapy and radiotherapy is typically associated with eventual tumor shrinkage, but this effect is frequently delayed. Many emerging therapies lead only to tumor stasis. Noninvasive biomarkers of drug delivery and molecular drug action are therefore essential in order to assess at the earliest possible time point localized drug activity and thus the likelihood of clinical response. The value of magnetic resonance spectroscopy (MRS) as a method to assess response will be presented and discussed.

Response to radiotherapy and DNA-damaging chemotherapy was shown several years ago to result in $^1$H and $^{31}$P MRS-detectable metabolic changes. In particular, the phospholipid precursor phosphocholine (PC), which is elevated in tumors compared to normal tissue, drops following treatment, frequently prior to tumor shrinkage (1-3). This observation can be explained in part by inhibition in cellular proliferation (4-7). $^1$H-MRS detectable modulation in lactate levels has also been reported as an indicator of response to treatment (8-10) consistent with a reversal of the Warburg effect. Elevation in the lipid signal, and in particular elevation in polyunsaturated fatty acids, has been observed by $^1$H-MRS and is associated with apoptosis, the program of cell death induced in many cases by chemotherapy and radiotherapy (10-14). Apoptosis also leads to a drop in cellular NADH levels (15, 16). Because NADH is a co-factor for the enzyme lactate dehydrogenase, DNA damage by chemotherapeutic agents, which causes PARP activation and NADH depletion, results in a reduction of the $^{13}$C MRS-detectable conversion of exogenous hyperpolarized pyruvate into hyperpolarized lactate (17, 18). The conversion of fumarate into malate has been shown as another hyperpolarized $^{13}$C MRS approach that can inform on response via necrotic cell death (18).

MRS has also been used to monitor the metabolic consequences of treatment with targeted therapies. An overall change in the $^1$H-MRS detectable metabolomic profile can be detected (19). Additionally, specific metabolic changes have been investigated in depth. PC and total choline-containing metabolites (tCho) drop following treatment with inhibitors of the phosphoinositide-3-kinase (PI3K) or the mitogen-activated protein kinase (MAPK) oncogenic signaling pathways as well as inhibitors of their common downstream effector hypoxia-inducible factor 1 (HIF-1) (20-26). This effect is likely mediated by inhibition of the expression of choline kinase, the enzyme responsible for PC synthesis (7, 24, 27). Inhibition of PI3K signaling also leads to a drop in the expression of several glycolytic enzymes, including lactate dehydrogenase, resulting in a decrease in
the hyperpolarized pyruvate conversion to lactate (26, 28). Interestingly, inhibition of heat shock protein 90, either directly or via reduction of histone deacetylase activity, leads in most cases to elevation in PC levels (29-32) recently shown to result from elevation in choline transport (33). In some cases an elevation in GPC has also been reported and is due to elevated phospholipase A2 activity (33-35). Finally, because the abnormal cancer metabolism is likely a factor in cancer development, anti-metabolites are entering clinical trials. Their effects can also be monitored by MRS. Inhibition of choline kinase resulted in the expected drop in MRS-detected PC levels (36). Inhibition of fatty acid synthase, the enzyme responsible for lipid synthesis, also led to a drop in PC (37).

In summary, several MRS-detectable metabolic changes have been observed following anticancer treatment. Whereas many of these are not specific to just one drug, they are nonetheless highly valuable as noninvasive longitudinal biomarkers that can inform on drug delivery and drug-target modulation to predict response and identify resistance.

References


