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Oxidative Phosphorylation Induces De Novo Expression of the MHC Class I in Tumor Cells through the ERK5 Pathway

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Most cancer cells use anaerobic-like glycolysis to generate energy instead of oxidative phosphorylation. They also avoid recognition by CTLs, which occurs primarily through decreasing the level of MHC class I (MHC-I) at the cell surface. We find that the two phenomena are linked; culture conditions that force respiration in leukemia cells upregulate MHC-I transcription and protein levels at the cell surface, whereas these decreases in cells forced to perform fermentation as well as in leukemia cells lacking a functional mitochondrial respiratory chain. Forced respiration leads to increased expression of the MAPK ERK5, which activates MHC-I gene promoters, and ERK5 accumulation in mitochondria. Respiration-induced MHC-I upregulation is reversed upon short hairpin RNA-mediated ERK5 downregulation and by inactive mutants of ERK5. Moreover, short hairpin RNA for ERK5 leukemia cells do not tolerate forced respiration. Thus, the expression of ERK5 and MHC-I is linked to cell metabolism and notably diminished by the metabolic adaptations found in tumor cells. The Journal of Immunology, 2010, 185: 3498–3503.

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Materials and Methods

Reagent and Abs

The following Abs anti–H2Kb-FITC, anti–H-2Kk-FITC, anti–H2Kd-PE, anti–CD19-FITC, anti–HLA-PE, and anti-cytochrome c were from BD Pharmingen (San Diego, CA). The Abs against ERK5, cytochrome c oxidase IV, and β-actin were from Cell Signaling Technology (Beverly, MA). The anti–HLA W632 and the anti–H2Dd ER-HB52 Abs used for Western blotting were generous gifts from Dr. Valerie Pinet (Institut de Génétique Moléculaire de Montpellier, Montpellier, France) and from Santa Cruz Biotechnology. The anti–H2Kb, anti–H-2Kk, anti–H2Kd, anti–HLA-A, -B, and -C Abs were from Serotec (Oxford, UK). The anti–H-2Kd PE, anti–HLA-PE, and anti-cytochrome c Abs were from Dako (Glostrup, Denmark). The IgG Abs were obtained from Santa Cruz Biotechnology.
Immunoblotting

Protein analysis by immunoblotting was performed essentially as described previously (11). Briefly, cells were washed with PBS and lysed in SDS Laemmli sample buffer (2% [w/v] SDS, 2% [v/v] glycerol, 25 mM Tris-HCl [pH 6.8], and 1% [v/v] 2-ME). Cell fractions were resuspended in SDS Laemmli buffer for a final 1% concentration. Extracts were boiled for 5 min, and proteins were separated by SDS-PAGE before electrotransfer on polyvinylidene difluoride membranes (Millipore, Bedford, MA). Membranes were blocked at room temperature for 1 h in TBST (140 mM NaCl, 10 mM Tris-HCl [pH 7.5], 0.05% [v/v] Tween 20), and 5% [w/v] lowfat milk powder) and incubated overnight at 4°C with the indicated Abs (diluted in blocking buffer or 5% BSA (w/v)-TBST). After several washes in TBST, the membranes were incubated for 1 h at room temperature with peroxidase-conjugated secondary Abs diluted in blocking buffer. After being washed with TBST, protein–Ab complexes were detected by chemiluminescence, using either the Pierce (Rockford, IL) or Millipore ECL Western blotting kit.

RNA isolation and quantitative RT-PCR experiments

RNA from 10 × 10^6 cells was isolated with the GenElute Mammalian Total RNA Miniprep Kit as described by the supplier (Sigma-Aldrich). Total RNA was subjected to DNase treatment using an RQI RNAse-free DNase (Promega). One microgram of each sample was reverse-transcribed into cDNA using a SuperScript III Reverse Transcriptase (Invitrogen, Carlsbad, CA) according to the supplier’s specifications. cDNAs were amplified using the SYBR Green PCR Master Mix (Invitrogen). Amplification products were detected by real-time PCR using the Multiplex Quantitative PCR System Mx3000P (Stratagene, La Jolla, CA) according to the manufacturer’s specifications. Measurements were carried out every 90 s at 95°C followed by 40 cycles of 95°C for 5 s, 60°C for 20 s, and 72°C for 30 s. For the quantification of gene expression, external standards were generated and selected using the Primer3 (version 0.4.0) program (18) and were subjected to DNase treatment using an RQ1 RNase-free DNase (Promega). One microgram of each sample was reverse-transcribed into cDNA using a SuperScript III Reverse Transcriptase (Invitrogen, Carlsbad, CA) and was subjected to PCR experiments according to the manufacturer’s specifications and normalized to the values of the housekeeping gene S26.

Cell survival and apoptosis assays

Cell survival was analyzed by changes in forward light scatter/side scatter of light or by tetramethylrhodamine ethyl ester staining as described previously (11, 19).

Confocal imaging

Immunofluorescence confocal images were acquired using a LSM 510 inverted laser-scanning microscope (Zeiss, Oberkochen, Germany). The extent of colocalization of two labels was determined using the “Colocalization” module of Imaris 5.0.2 software, 64-bit version (Bitplane, St. Paul, MN; www.bitplane.com). The program uses an iterative procedure (20) to determine an intensity threshold (in the 0–255 scale of pixel intensity) for each of the two labels. Voxels with intensities above this threshold are considered to be above the background (20).

Statistical analysis

The statistical analysis of the difference between means of pairs of samples was performed using the paired t test. The results are given as the CI (p). All of the experiments described in the figure legends were performed at least three times with similar results.

Results

When glucose is no longer available, cells are forced to use alternative energy substrates, such as Gln. Gln oxidation, or glutaminolysis, generates ATP through OXPHOS (21,22). We wondered whether forcing cancer cell lines to use this pathway would affect MHC-I expression. To test this, the mouse B leukemia cell line L1210 was changed to glucose-free culture medium supplemented with 10 mM galactose and 4 mM Gln, hereafter called OXPHOS medium (Fig. 1A). Galactose allows cells to synthesize nucleic acids through the pentose phosphate pathway (21,22). Mitochondrial function was absolutely required under these conditions, as expected (21,22), because the mitochondrial proonophore carbonyl cyanide-p-trifluo-

Cell lines and culture conditions

The leukemic T cell line Jurkat and the murine leukemic B L1210 cell line were grown in RPMI 1640-Glutamax (Life Technologies, Rockville, MD) supplemented with 6% FBS. In certain experiments, cells were incubated in RPMI 1640 (Life Technologies 11879) that contains 2 mM glutamine (Gln) but no glucose. This media was supplemented with 25 mM glucose (glucose medium), 10 mM galactose, 2 mM Gln (Gln medium), or 12.5 mM each pyruvate plus malate (pyruvate medium). L929p0 cells have been described (13). EL4p0 cells were prepared using a similar protocol (14); selective elimination of mitochondrial DNA was achieved by long-term exposure to low concentrations (50 ng/ml) of ethidium bromide. The selection and culture medium of EL4p0 cells was also supplemented with glucose, 5.5 mM, sodium pyruvate (0.1 mg/ml), and uridine (50 pg/ml). L929p0 cells do not show modification on expression of several other proteins (13). In EL4-p0 cells, we did not find changes in expression of X-linked inhibitor of apoptosis protein, BCL-2 interacting domain, cytochrome c, apoptosis-inducing factor, Cu2-Zn superoxide dismutase, caspase 3, caspase 9, or tubulin (14).

Plasmids

The expression vectors for ERK5, a constitutively active MEK5 mutant (S313DT/T317ID, termed MEK5D), and β-galactosidase, the pSUPER expression vector for GFP alone or GFP plus short hairpin RNA (shRNA) for ERK5 (shERK5), and the pSIREN-RetroQ-puro (BD Biosciences, San Jose, CA) retrovector proteins for shERK5 and control have been described (11). The expression vectors for the nonphosphorylatable ERK5 mutant (ERK5AEF, the activating TEY motif mutated to AEF) in pC14a and the catalytically inactive ERK5 kinase (K84 mutated to M) in pLZR were generous gifts from Dr. Axel Ullrich (Max-Planck Institute of Biochemistry, Martinsried, Germany) and Dr. Atanasio Pandiella (Centro de Investigacion del Cancer, Instituto de Biologia Molecular y Celular del Cancer/CSIC-Universidad de Salamanca, Salamanca, Spain), respectively. The MHC-I promoter constructs derived from the swine class I gene Pd-1 (15) and the human HLA-A gene (16) have been described.

Transient transfection and stable cell line generation

Jurkat cells in the logarithmic growth phase were transfected with the indicated amounts of plasmid by electroporation (11). In each experiment, cells were transfected with the same total amount of DNA by supplementing with the empty vector. Cells were incubated for 10 h at room temperature with the DNA mix and electroporated at 260 mV 960 μF in 400 μM RPMI 1640. Stable cell lines were generated as described previously (11). Briefly, cells are plated at 1.5 × 10^4 cells per milliliter. One milliliter of a supernatant from 293T cells expressing the retroviral vectors for shERK5 or control sequence were added after plating. Three days later, cells were cultured with 2.5 μg/ml puromycin (Sigma-Aldrich, St. Louis, MO). After 1 wk, surviving cells were isolated and kept on selection medium until used.

Reporter assay

In all of the experiments, cells were transfected with a β-galactosidase reporter plasmid (17). Transfected cells (10^6) were harvested at 2 and washed twice with PBS. Cells were lysed in 100 μl luciferase lysis buffer (Promega, Charbonnières, France), and luciferase assays (40 μl) were performed according to the manufacturer’s instructions (Promega) using a luminometer (Berthold, Bad Wildbad, Germany). For β-galactosidase assays, 40 μl lysates were added to 200 μl β-galactosidase assay buffer (50 mM phosphate buffer [pH 7.4], 1 mg/ml ortho-nitrophenyl-β-galactoside, 1 mM MgCl2, and 50 mM 2-ME), and the absorbance was measured at 405 nm. The results are expressed as luciferase units normalized to the corresponding β-galactosidase activity. The expression level of the transfected proteins was routinely controlled by immunoblot analysis.

FACS analysis

For flow cytometry, cells (1 × 10^6) were stained for 20 min at room temperature with the indicated FITC-, PE-, or allophycocyanin-conjugated Abs in 200 μl PBS. Cells were washed and analyzed on a FACSCalibur flow cytometer (BD Biosciences) using CellQuestPro software (BD Biosciences). For total MHC-I expression in permeabilized cells, L1210 cells growing in various media were incubated for 15 min with anti-H2K β,PE- or anti-H2K β,PE- (total MHC-I expression) or control IgG-PE (membrane MHC-I expression). After being washed in PBS, cells were analyzed by FACS. Mitochondrial activity and mitochondrial content were analyzed by incubating cells with Mitotracker Red (100 nM) and NAO (1 μM) for 20 min at 37°C. Cells were analyzed by FACS.

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PBS, and fixed with 2% paraformaldehyde for 15 min. Next, they were analyzed by FACS.

Tracker Red (100 nM) and NAO (1

Proteins was routinely controlled by immunoblot analysis. The results are expressed as luciferase units normalized to the corresponding β-galactosidase activity. The expression level of the transfected proteins was routinely controlled by immunoblot analysis.

For flow cytometry, cells (1 × 10^6) were stained for 20 min at room temperature with the indicated FITC-, PE-, or allophycocyanin-conjugated Abs in 200 μl PBS. Cells were washed and analyzed on a FACSCalibur flow cytometer (BD Biosciences) using CellQuestPro software (BD Biosciences). For total MHC-I expression in permeabilized cells, L1210 cells growing in various media were incubated for 15 min with anti-H2K β,PE- or anti-H2K β,PE- (total MHC-I expression) or control IgG-PE (membrane MHC-I expression). After being washed in PBS, cells were analyzed by FACS. Mitochondrial activity and mitochondrial content were analyzed by incubating cells with Mitotracker Red (100 nM) and NAO (1 μM) for 20 min at 37°C. Cells were analyzed by FACS.
romethoxyphenylhydrazone induced massive cell death in <24 h without affecting the viability of cells growing in glucose. Interestingly, cells growing in OXPHOS medium for 3 d showed a 3-fold increase in MHC-I expression, as analyzed by flow cytometry (Fig. 1A). Further incubation for 2 or 4 d led to a minor increase (Fig. 1A). Therefore, we used 3-d incubations for subsequent studies. Cells growing in the presence of pyruvate and malate as respiratory substrates showed a similar increase (Fig. 1A, right panel) and also were sensitized to carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (data not shown). The expression of the B cell Ag CD19 (Fig. 1B, left panel) did not change in the different media. These results were statistically significant (Fig. 1B, right panel). Dichloroacetate (DCA), a pyruvate dehydrogenase kinase 1 inhibitor (23), activates pyruvate dehydrogenase (24). This forces pyruvate to enter the Kreb’s cycle and therefore respiration even in high-glucose media (24). DCA increased MHC-I expression in the presence of 25 mM glucose (Fig. 1C), whereas expression of CD19 was unaltered (Fig. 1C, left panel). Thus, the increase in MHC-I levels is not an artifact of glucose deprivation inhibiting glycolysis, because this continues in the presence of DCA, although at a lower rate.

The human leukemia T cell line Jurkat also showed an increase in MHC-I expression in OXPHOS media but not in MHC-I chain-related gene A (Fig. 1D). Importantly, MHC-I upregulation under OXPHOS conditions was reversible. L1210 cells in glucose (Fig. 1E, left panel) or Jurkat (Fig. 1E, right panel) cells with an OXPHOS medium-driven increase in MHC-I expression were returned to medium containing glucose. MHC-I levels started decreasing within 48 h and by 72 h approached those seen in cells continuously growing in glucose (Fig. 1E). This makes it highly unlikely that the effect that we observe reflects an irreversible phenomenon induced by OXPHOS growth conditions; instead, it confirms the link between growth conditions and MHC-I expression.

To further support this idea, we analyzed MHC-I expression in L929p0 and EL4p0 cells, which lack a functional mitochondrial respiratory chain (13, 14). Importantly, both show a strong decrease in MHC-I levels at the cell surface (Fig. 1F). Thus, the metabolic status of tumor cells affects expression of MHC-I at the plasma membrane, which requires functional mitochondria. This expression is regulated at different levels, including transcription (5). Indeed, L1210 cells growing in OXPHOS media for 2 d showed higher mRNA expression of both the L chain (β2-m) and the H chain of the class I molecule H-2Kb (Fig. 2A). Accordingly, Jurkat cells growing in those media increased expression of a reporter gene controlled by the promoter of the MHC-I gene PD-1 (Fig. 2B) or the proximal promoter of the human HLA-A gene (Fig. 2B, right panel). This effect was not due to glucose deprivation, because addition of DCA to glucose media also activated the PD-1 promoter (Fig. 2B). Our Glc media contained 5% nondialyzed FBS and therefore ~0.5 mM glucose. To block glycolysis, we used 2-deoxyglucose, which also increased the expression of the PD-1 promoter in all media (Fig. 2B).
The increased transcription of class I molecules correlated with higher total expression of MHC-I molecules in cells growing in OXPHOS media (Figs. 2C, 3A). Therefore, respiration induces de novo expression of MHC-I molecules and not just an increase in their translocation to the plasma membrane.

ERK5 controls MHC-I expression in leukemia cells (12). Interestingly, OXPHOS media increased ERK5 protein expression in our system (Fig. 3A). Moreover, transfection of ERK5 and MEK5D activated the PD-1 gene reporter, in agreement with our previous results (12), and synergized with all of the OXPHOS conditions tested (Fig. 3B). ERK5 subcellular localization depends on the cell type investigated; inJurkat cells, immunofluorescent staining showed that ERK5 localized in the cytosol, including a compartment reacting with the mitochondrial marker MitoTracker Red (Fig. 4A). Quantitative measurement using Imaris software (St. Paul, MN) showed that 20% of ERK5 colocalized with cytochrome c. Cell fractionation analyses showed that, although the major portion of ERK5 protein was in the soluble cytosolic fraction, a significant amount was associated with mitochondria (Fig. 4A, right panel).

OXPHOS conditions increased the number of mitochondria in L1210 cells (Fig. 4B), as measured by staining with MitoTracker Red as well as with NAO, which binds mitochondria independently of their membrane potential. This correlated with higher ERK5 expression (Fig. 3) that, like MHC-I expression (Fig. 1E), was reversible (Fig. 4C). In addition, Cytochrome c extensively colocalized with ERK5 (Fig. 4E), the majority of which was now found in the mitochondrial fraction (Fig. 4D). Thus, OXPHOS media induced an increase in ERK5 that associated predominantly with mitochondria. In retinal pigment epithelial cells under normoxia, ERK5 regulates a series of genes also induced in hypoxia via activation of HIF-1x (6). These results implicate ERK5 in transcriptional regulation of several metabolic pathways.

To investigate the role of ERK5 in OXPHOS, we generated leukemic cells stably expressing shERK5 or a scrambled control shRNA (shSCR), shERK5 L1210 and Jurkat cells showed a 60% reduction of ERK5 levels (Fig. 5A). shSCR as well as wild-type cells survived in OXPHOS medium (Fig. 5B), although they grew more slowly than those in glucose medium (22). In contrast, shERK5 cells showed increased cell death under OXPHOS conditions (Fig. 5B), a sign of impaired mitochondrial function. These cells also show decreased MHC-I expression (12), further supporting the idea that functional mitochondria are essential for MHC-I expression (e.g., Fig. 1F). In addition, OXPHOS-induced activation of the PD-1 promoter was blocked by expression of shERK5 as well as vectors encoding distinct dominant-negative versions of ERK5 (ERK5KM and ERK5AEF) (Fig. 5C). Thus, the ERK5 pathway is required for MHC-I transcriptional activation.

Discussion

The role of metabolic alterations in malignant transformation and cancer progression is increasingly appreciated after a long dormant period following the initial observations by Warburg. Somewhat similarly, the long-standing notion of cancer immunosurveillance has finally gained acceptance (4). Our results show that the ERK5 MAPK cascade, which is essential for “normal” metabolism and plasma membrane expression of MHC-I, is a nexus between both processes.

Nontransformed cells growing under normal conditions (i.e., with glucose as the primary energy source) will generate ATP by
respiration and express normal levels of MHC-I. Tumor cells principally use the less efficient but more rapid process of fermentation to generate ATP, which potentially offers a selective advantage to rapidly growing tumor cells. Our results suggest that this metabolic alteration has a second advantage for leukemia and potentially other tumor cells: strongly reduced MHC-I expression and thereby less exposure of TAAs. We show that forcing leukemia cells to perform respiration leads to increased MHC-I expression at the RNA and protein level. This is observed using different approaches, and importantly it is fully reversed when the cells again have the capacity to metabolize glucose. Moreover, the different conditions have similar effects on expression of a MHC-I reporter gene, strongly indicating that a key level of regulation is transcriptional. Our data here strongly implicate the ERK5 cascade therein; cotransfection of vectors expressing the core components of this cascade, namely, MEK5 and ERK5, enhances transcriptional induction of the MHC-I reporter gene byOXPHOS conditions, an effect that is blocked by inactive mutants of ERK5. Moreover, forced respiration also leads to increased levels of endogenous ERK5, and shRNA-mediated knockdown of ERK5 decreased endogenous and exogenous MHC-I promoter activation byOXPHOS. This suggests that the ERK5 cascade directly targets the MHC-I promoter; both ERK5 and its downstream effector kinase ribosomal S6 kinase regulate transcription factors, such as myocyte enhancer factor-2, c-Myc, NF-κB, and CREB, by phosphorylation. However, given the complexity of MHC-I transcriptional regulation, where distinct promoter elements drive constitutive expression, the response to IFN-γ, and induction in T cells, further analyses will be required to identify the DNA

FIGURE 4. ERK5 colocalizes in mitochondria in leukemic cells. A. Left panel, One million Jurkat cells were fixed with paraformaldehyde and stained with MitoTracker Red, ERK5, and Hoechst. Cells were analyzed by confocal microscopy (original magnification ×1000). Right panel, Jurkat cell extracts were fractionated in m and c fractions to investigate the relative localization of different proteins. Fifty micrograms of these fractions or whole-cell extract were analyzed for ERK5 localization. The purity of the fractions was analyzed using linker of activated T cells, topoisomerase, and cytochrome c oxidase IV as markers of cytosol, nuclei, and mitochondria, respectively. B. One million Jurkat cells were placed in media containing glucose (25 mM) or Gln (4 mM) plus galactose (10 mM). Five days later, mitochondrial content was analyzed by FACS using NAO or MitoTracker Red. C. L1210 cells growing in glucose (1) were incubated for 3 d in Gln media. Then, cells were incubated in either Gln (2) or glucose (3) media for an additional 3 d, and protein expression was analyzed by Western blot. D. Respiration induces ERK5 translocation to mitochondria. L1210 cells were incubated for 3 d in glucose (1) or Gln (2) media and subjected to subcellular fractionation as in A. E. Cells incubated as in D were stained as in A, but cytochrome c (in red) was used to label mitochondria. The bar represents 20 μm. Arrows show ERK5 accumulation in mitochondria, which is enhanced byOXPHOS media. c, cytosol; m, mitochondria.

FIGURE 5. ERK5 is essential for survival in OXPHOS media. A. Down-regulated ERK5 expression in shERK5-expressing cells. Protein expression in whole-cell extracts was analyzed by Western blotting with the corresponding Abs. B. Downregulation of ERK5 expression impairs cell survival inOXPHOS media. Fifty thousand (glucose) or 150 × 10⁶ (OXPHOS) L1210 or Jurkat shSCR (white bars) or shERK5 (gray bars) cells were incubated for 72 h in the different media. Survival was assayed as described in Materials and Methods. The data are presented as the mean ± SD of at least three independent experiments and were evaluated using the Student t test. *p < 0.005; ** p < 0.0005 compared with shSCR cells. C. ERK5 activity is essential forOXPHOS-induced MHC-I expression. Ten million Jurkat cells were transfected with the following: 5 μg of expression vectors for ERK5AEF (a nonphosphorylatable mutant) and ERK5KM (a kinase death mutant), a shERK5, 2.5 μg of the reporter gene PD-1-Luc, and 1 μg of the β-galactosidase expression vector. One day later, cells were placed in media containing glucose (25 mM) or OXPHOS media. Forty-eight hours later, lysates were prepared and analyzed for luciferase and galactosidase activity. The relative luciferase units represent the luciferase/β-galactosidase ratio. The data are presented as the mean ± SD of at least three independent experiments and were evaluated using the Student t test. *p < 0.05; **p < 0.005 compared with pcDNA-transfected cells.
sequences and transcriptional regulators that mediate its activation by the ERK5 cascade.

Although the mechanism that links respiration to MHC-I regulation remains to be characterized, one component appears to be ERK5. Its expression level is increased by OXPHOS conditions, after which a significant portion is found to be associated with mitochondria. At present, we do not possess the genetic tools to generate leukemia cells where ERK5 is uniquely targeted to mitochondria, so the functional significance of this observation remains unclear. Nevertheless, diminishing ERK5 levels in leukemia cells via shRNA expression leads to increased cell death under OXPHOS conditions, which implies a role for ERK5 in the control of mitochondrial respiration. This is not surprising, because Jurkat cells stably expressing shERK5 show misregulation of a broad class of metabolic genes (data not shown). Moreover, these data clearly demonstrate a role for the ERK5 cascade in the survival of leukemia cells forced to perform respiration. The link between ERK5 and cell survival is not new. Conditional knockout of ERK5 in adult mice leads to death from vascular failure arising from massive apoptosis of endothelial cells (25). Both ERK5 knockdown and blocking cascade activation with kinase-dead mutants of ERK5 and MEK5 enhance the sensitivity of several cancer-derived cell lines to apoptotic signals and compromise survival in both normal and cancer-derived cell lines (9). Our observations offer a specific context where ERK5 is required for survival of leukemia cells, namely, one linked to metabolism.

Changes in metabolism would seem most likely to induce oxidative stress, which activates the ERK5 cascade in several cellular contexts (26). However, we do not observe an increase in activating phosphorylation of ERK5 in OXPHOS conditions, even though ERK5 with kinase activity is required for MHC-I activation. Moreover, the antioxidants glutathione and N-acetyl-l-cysteine fail to block MHC-I upregulation. Although unlikely, we cannot rule out that other reactive oxygen species insensitive to these agents play a role in the process. It is also possible that the time points that we evaluated fell outside the period of ERK5 activation, which is transient in cells subjected to oxidative stress. L1210 cells have been cultivated in OXPHOS media for >3 mo. These cells show no sign of apoptosis, stress, or altered expression of several surface markers, with the exception of MHC-I levels that remain well above those on L1210 cells maintained in glucose medium. Nevertheless, shifting these cells from OXPHOS to glucose media led to decreased MHC-I expression in 3–5 d, demonstrating that the process is reversible even after several months. Future studies will determine the mechanism by which the metabolic state of tumor cells controls the ERK5–MHC-I regulatory module and the role that it might play in avoiding the adaptive immune response. Furthermore, our data suggest that a novel clinical approach to reverse this process would be the use of agents that force respiration in leukemia (and other cancer) cells, initially in vitro and eventually in vivo. This would not be expected to affect normal cells but only cancer cells “addicted” to glucose; the resulting increase in ERK5 and MHC-I levels would drive the patient’s own immune system to mount an efficient anti-cancer response.

Disclosures

Our results are covered by patent application FR 08/02809, submitted in France by M.V., Johan Garaude, Chantal Jacquet, S.C., GdB., and R.A.H.

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