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From the nucleus to the mitochondria and back

The odyssey of a multitask STAT3

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STAT3, a member of the signal transducers and activators of transcription (STAT) family, is constitutively activated by phosphorylation on tyrosine 705 in a high percentage of tumors and tumor-derived cell lines of both liquid and solid origin, downstream of cytokines, growth factors and oncogenes.[1] Tumor cells often become addicted to STAT3, as shown by the observation that interference with its transcriptional activity often triggers growth arrest and/or cell death. Importantly, STAT3 can also be phosphorylated on Serine 727 downstream of a number of stimuli leading to the activation of MAP kinases including RAS signaling.[2] Although STAT3-mediated gene expression signature is mostly consistent with tumor cell survival and proliferation,[3] it varies in different tumor types, and a core activity determining addiction to STAT3 by a wide spectrum of biologically distinct tumors has not yet been identified.

To address this point, we have generated knock-in mice expressing physiological levels of the constitutively active STAT3C mutant form. STAT3C cooperates with the rat NEU oncogene triggering the production of more invasive mammary tumors via upregulation of the focal adhesion protein CTEN.[4] In order to dissect the molecular functions of constitutively activated STAT3, we have analyzed primary mouse embryonic fibroblasts (MEF) derived from $STAT3^{C/C}$ or $STAT3^{WT/WT}$ mice.[5] $STAT3^{C/C}$ MEFs showed increased proliferation, protection from apoptotic stimuli, decreased production of Reactive Oxygen Species (ROS) and delayed physiological senescence. Intriguingly, gene expression profiling revealed that $STAT3^{C/C}$ cells downregulated nuclear-transcribed mitochondrial genes, including many encoding for proteins belonging to the Electron Transport Chain (ETC) complexes, and upregulated mRNAs involved in glycolysis, first of all Hypoxia Inducible Factor (HIF)-1α.

Recently, STAT3 was shown to play an unconventional role in mitochondria.[6-8] Mitochondrial STAT3 (mSTAT3) appears to sustain ETC basal activity under normal or RAS-transformed conditions, supporting RAS-dependent oncogenic transformation,[6,7] and it was suggested to act as a negative regulator of the Mitochondrial Permeability Transition Pore (MPTP), thus mediating cardioprotection after ischemia/reperfusion.[8] Ser727 is required for mSTAT3 functions, while Tyr705, nuclear localization or DNA binding activity are dispensable. Indeed, activated RAS triggers Ser-phosphorylation rather than the conventional phosphorylation on Tyr, which in contrast confers nuclear localization and transcriptional activity and drives nuclear (n) STAT3 functions.[3] STAT3C mitochondrial localization was normal and mSTAT3 activities appeared to be preserved in the $STAT3^{C/C}$ cells.[5] Nevertheless, mitochondrial activity and ATP production were reduced and could not be rescued by HIF-1α silencing. Moreover, preliminary data suggest that the defective expression of several ETC proteins can be rescued upon STAT3 silencing (Poli V and Wieckowski M, unpublished data), supporting the idea that the action of constitutively activated STAT3 on mitochondria is dominant and occurs primarily in the nucleus via direct or indirect transcriptional downregulation of mitochondrial genes. Always in the nucleus, the constitutively activated STAT3 upregulates transcription of the HIF-1α gene, leading to HIF-1α-mediated upregulation of glycolysis including high glucose consumption and dependence for survival.

Thus, activated nSTAT3 acts as a master regulator of the metabolic switch from mitochondrial respiration to glycolysis occurring in most cancer cells and known as the "Warburg effect,"[9] by promoting HIF-1α-dependent aerobic glycolysis while depressing mitochondrial activity in a HIF-1α-independent fashion. This switch is an important component of STAT3 pro-oncogenic activities, since inhibition of STAT3 tyrosine phosphorylation and dimerization via the small molecule inhibitor S3I in several STAT3-dependent tumor cell lines downregulates glycolysis and enhances mitochondrial activity prior to leading to growth arrest and cell death, both in vitro and in vivo.[5] Moreover, primary $STAT3^{C/C}$ MEFs become transformed and tumorigenic when immortalized via the 3T3 protocol, suggesting that constitutively active STAT3 can provide a first hit in the multistep transformation process (Demario M, et al., submitted).

As depicted in **Figure 1**, at least two functionally distinct STAT3s exist. nSTAT3 acts in a conventional way to regulate gene transcription as a Tyr-phosphorylated dimer, while mSTAT3 works unconventionally to regulate mitochondrial functions, presumably requiring phosphorylation on Ser727. mSTAT3 preserves ETC activity both under basal and RAS-transformed conditions, and may provide protection from

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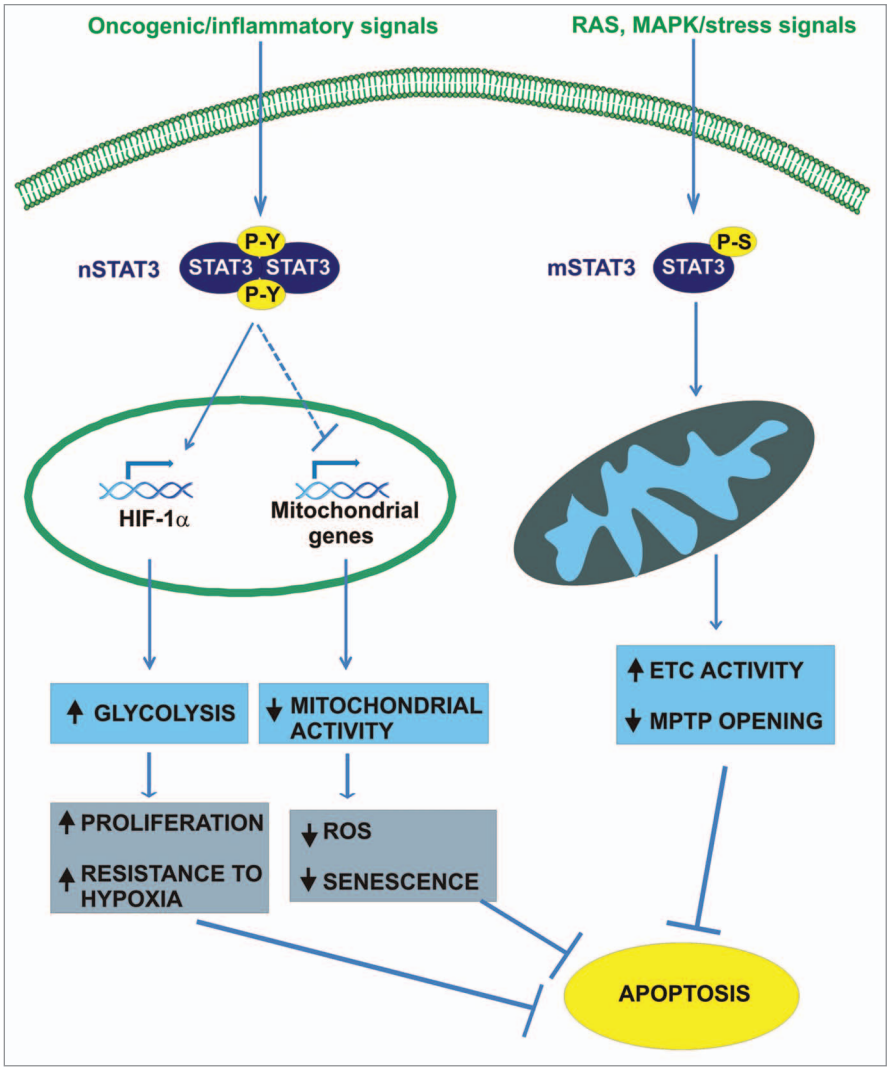

Figure 1. Converging roles of nuclear (n) and mitochondrial (m) STAT3. Different signals can selectively trigger STAT3 phosphorylation. Tyr-phosphorylated nSTAT3 (P-Y) mediates, among other effects, the upregulation of HIF-1α transcription and the downregulation of mitochondrial genes, thus triggering faster proliferation,[10] decreased ROS production and resistance to apoptosis. On the other end, Ser-phosphorylated mSTAT3 (P-S) preserves ETC activity and regulates MPTP opening, ultimately also leading to apoptosis protection.

apoptosis upon stresses such as ischemia/reperfusion by regulating MPTP opening.[6-8] Our data suggest that nSTAT3, when constitutively transcriptionally activated as it occurs downstream of oncogenic and inflammatory signals that trigger its tyrosine phosphorylation, promotes aerobic glycolysis and lowers cellular respiration, resulting in enhanced proliferation, resistance to hypoxia, glucose dependence and, importantly, decreased ROS production and resistance to apoptosis and senescence. Thus, although regulated downstream of different signals under distinct physiological or pathological conditions, nSTAT3 and mSTAT3 finally converge to enhance cell survival and protection from apoptosis via specific regulation of mitochondrial functions. Among other outstanding issues, it will be important to assess if and how the altered relative levels of Tyr-phosphorylated or Ser-phosphorylated STAT3 brought about by different oncogenic signals and inflammatory/stress conditions, altering the balance between nuclear and mitochondrial STAT3, can lead to an altered metabolic output.

References

1. Pensa S, et al. JAK-STAT Pathway in Disease 2009; 100-21.
2. Ceresa BP, et al. Endocrinology 1997; 138:4131-7; PMID:9322921; DOI:10.1210/en.138.10.4131.
3. Yu H, et al. Nat Rev Cancer 2009; 9:798-809; PMID:19851315; DOI:10.1038/nrc2734.
4. Barbieri I, et al. Cancer Res 2010; 70:2558-67; PMID:20215508; DOI:10.1158/0008-5472.CAN-09-2840.
5. Demaria M, et al. Aging (Albany NY) 2010; 2:823-42; PMID:21084727.
6. Wegrzyn J, et al. Science 2009; 323:793-7; PMID:19131594; DOI:10.1126/science.1164551.
7. Gough DJ, et al. Science 2009; 324:1713-6; PMID:19556508; DOI:10.1126/science.1171721.
8. Boengler K, et al. Basic Res Cardiol 2010; 105:771-85; PMID:20960209; DOI:10.1007/s00395-010-0124-1.
9. Warburg O. Science 1956; 123:309-14; PMID:13298683; DOI:10.1126/science.123.3191.309.
10. Vander Heiden MG, et al. Science 2009; 324:1029-33; PMID:19460998; DOI:10.1126/science.1160809.