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MINI-REVIEW

Imaging mitochondrial redox potential and its possible link to tumor metastatic potential

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Abstract Cellular redox states can regulate cell metabolism, growth, differentiation, motility, apoptosis, signaling pathways, and gene expressions etc. A growing body of literature suggest the importance of redox status for cancer progression. While most studies on redox state were done on cells and tissue lysates, it is important to understand the role of redox state in a tissue in vivo/ex vivo and image its heterogeneity. Redox scanning is a clinical-translatable method for imaging tissue mitochondrial redox potential with a submillimeter resolution. Redox scanning data in mouse models of human cancers demonstrate a correlation between mitochondrial redox state and tumor metastatic potential. I will discuss the significance of this correlation and possible directions for future research.

Keywords Cancer aggressiveness · Fluorescence · Redox scanning · NADH · FAD or flavoprotein

Introduction

As a hallmark of cancer, abnormal metabolism has taken the center stage of research in recent years (Pedersen 2007; Christofk et al. 2008; Hsu and Sabatini 2008; Cairns et al. 2011; Hanahan and Weinberg 2011; Koppenol et al. 2011; Lisanti et al. 2011). Most cancers exhibit the Warburg effect – increased glucose consumption even in the presence of oxygen, on which FDG-PET (fluorine-18-2-D-deoxyglucose positron emission tomography) is based to stage tumors and monitor treatment response (Quon and Gambhir 2005; Mac Manus and Hicks 2008). In addition, mitochondrial bioenergetic/genetic abnormalities have been shown to mediate carcinogenesis and tumor progression (King et al. 2006; Modica-Napolitano et al. 2007; Mayevsky 2009; Kaelin and Thompson 2010). Genetic mutations have been identified in cancer patients for certain mitochondrial metabolic enzymes in the TCA cycle including isocitrate dehydrogenase, succinate dehydrogenase and fumarase (Thompson 2009). The expressions of genes or activities of proteins known to drive tumor progression such as Myc/HIF1α/p53 have been shown to regulate cellular metabolism including mitochondrial metabolism (Dang 1999; Semenza 2010; Cairns et al. 2011). On the other hand, tumor microenvironment and metabolism may be upstream regulators of signaling pathways (Hsu and Sabatini 2008). Therefore, it has become increasingly important to understand the interwined relationship among tumor signaling pathways, metabolism, and microenvironment.

Maintenance of redox state homeostasis has been regarded as important for cancer cells (Dorward et al. 1997; Grek and Tew 2010; Cairns et al. 2011; Locasale and Cantley 2011). As a matter of fact, tremendous research studies (Puppi and Dely 1983; Dorward et al. 1997; Adler et al. 1999; Nkabyo et al. 2002; Weir et al. 2002; Cook et al. 2004; Olschewski et al. 2004; Agarwal and Auchus 2005; Ido 2007; Sattler et al. 2007; Banerjee 2008; Ying 2008; Gough 2009; Maccarrone and Brune 2009; Pani et al. 2009; Sarsour et al. 2009; Grek and Tew 2010; Ishimoto et al. 2011) have demonstrated or implicated redox state as a key mediator of many cellular functions and activities including metabolism, growth, differentiation, cell cycle, motility/invasion, apoptosis, survival, immunological response, oxidative stress, gene transcription, and signaling (Fig. 1). Some studies have implied a connection between the redox potentials (or NADH levels) and the metastatic potential of cancers (Zhang et al. 2006; Ishikawa et al. 2008b; Pani et al. 2009; Pelicano et al. 2009; Grek and Tew 2010). Reactive oxygen species (ROS) are known to cause oxidative stress on proteins, lipids, DNA/RNAs and also act as signaling molecules to drive cancer cell motility/invasion and tumor progression. ROS can

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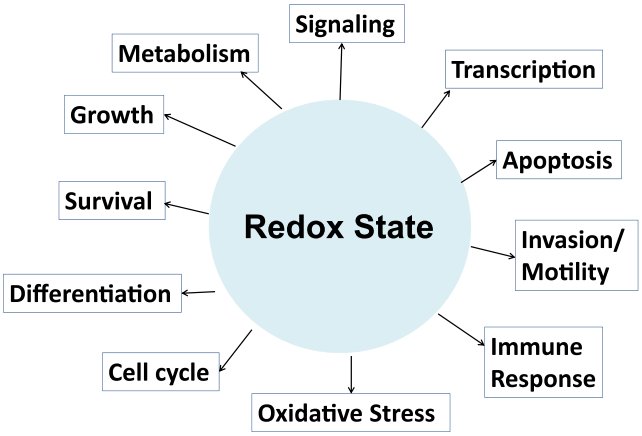

Fig. 1 Important roles of redox state in biology

induce a higher risk of metastasis either by causing more DNA mutagenesis or regulating tumor progressions directly by enhancing cell invasion and metastasis. A mitochondrial DNA mutation encoding a subunit of NADH dehydrogenase (complex I) was shown to control the development of metastasis in animal models by generating more ROS, which, in turn, directly regulates certain nuclear genes that promote metastasis (Ishikawa et al. 2008a, b). However, a high level of ROS or oxidants does not necessarily indicate more oxidized redox potential. It has been known that tumors with high levels of ROS are often counter balanced with high levels of reductants such as vitamin C, reduced glutathinone (GSH) and NADPH (Hyodo et al. 2006; Pelicano et al. 2009; Pani et al. 2010; Keshari et al. 2011). It is the balance between oxidants and reductants that define the cellular redox potential. Still redox potential is a complex issue due to multiple intracellular redox systems and their dependence on subcellular compartments (cytosol, nuclear, mitochondrion, etc.). Currently the relationship between cellular redox potential and cancer metastatic potential is far from clear.

Most prior work on redox status was done on the molecular and cellular levels under in vitro conditions or on tissue lysates. To investigate the role of redox potential in tumor progression, it is necessary to image the redox status and its spatial distribution in tissue. The tissue heterogeneity in functional/metabolic/genomic status has been regarded as an important characteristic for malignancy (Gaustad et al. 2005; Schroeder et al. 2005; Gerlinger et al. 2012; Shah et al. 2012). Intra-tumor heterogeneity has been shown to be an important factor for studying tumor metastasis (Nowell 1976; Fidler and Kripke 1977; Fidler and Hart 1982). The heterogeneity in a tumor metabolic microenvironment can occur on a small distance <1 mm (Mueller-Klieser et al. 1991; Li et al. 2009b; Xu et al. 2010). Therefore, effective sub-millimeter imaging methods are needed to measure the tumor redox state in vivo/ex vivo. Redox imaging on the basis of the fluorescence signals from NADH and flavoproteins is the only clinically-translatable method that can achieve 3D imaging of the tissue mitochondrial redox state at a submillimeter resolution.

In this mini-review we will cover some basic biological roles of NAD(H) and flavins, and the principles and methodology of mitochondrial redox imaging. We will then review the work studying the link of mitochondrial redox potential to tumor metastatic potential using the redox imaging. In the end, we will discuss the significance of these studies in terms of basic research and clinical management for cancer.

NAD(H), flavins and mitochondrial redox imaging

As universal free energy carriers in bioenergetics, NAD^+ (oxidized nicotinamide adenine di-nucleotides) and NADH mediate a number of oxidation-reduction reactions along pathways of energy metabolism. By controlling glycolysis in the cytosol and the Krebs cycle in mitochondria, the redox potential NAD^+/NADH is linked to the phosphorylation potential [ATP]/([ADP]·[Pi]) in living tissues and provides a key parameter for the metabolic control of normal and diseased phenotypes (Veech 2006). In addition, NAD^+/NADH is a key component in cellular redox homeostasis as NAD(H) is coupled to NADP(H) by transhydrogenase activity (Lemasters and Nieminen 2001) and, thus, can indirectly affect the oxidation-reduction couples of glutathione and thioredoxin systems as well (Banerjee 2008). These redox couples and related redox-sensitive enzymes may affect almost all major signaling pathways including p53, PI3K and MAPK (Adler et al. 1999; Olovnikov et al. 2009). Accumulating evidence has shown that NAD^+ is also a key signaling molecule serving as a precursor to calcium-releasing agents and a substrate for protein modification of transcription factors by PARP (poly-ADP-ribosylation polymerase) (Banerjee 2008). NAD^+ can mediate many cellular activities including signaling, reactive oxygen species (ROS) generation, growth, differentiation, survival, and apoptosis (Ziegler 2005; Orrenius et al. 2007; Ying 2008).

In addition to NAD(H), another group of redox-important molecules flavin nucleotides including flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) also play important roles in various biological processes including metabolism and signaling events (Lehninger et al. 1993; Taylor et al. 2001; Senda et al. 2009; Becker et al. 2011) FAD or FMN are coenzymes or prosthetic groups for various flavoproteins including the NADH dehydrogenase (complex I) and pyruvate dehydrogenase in mitochondria. These flavoproteins are quite often coupled with NAD^+/NADH. $FADH_2$ is also a free energy carrier in electron transport and the FAD-coupled redox potential FAD/$FADH_2$ regulates key reactions in the TCA cycle, oxidative

phosphorylation, and fatty acid metabolism (Lehninger et al. 1993). Both $FADH_2$ and NADH levels may regulate the ROS generation in mitochondria. Flavin prosthetic groups also induce redox-dependent conformational and functional changes in flavoproteins which are important for protein transcription, signaling pathways and environmental adaptation (Taylor et al. 2001; Senda et al. 2009; Becker et al. 2011).

The roles of NADH, flavins, and mitochondrial redox potential NAD^+/NADH or FAD/$FADH_2$ in tumor progression to metastasis are not clear. However, the fluorescence signals from these molecules (NADH and FAD) enable the development of the mitochondrial redox imaging, a useful tool to investigate these questions.

Dr. Chance and coworkers have pioneered in and made major contributions to using endogenous fluorescence signals of NADH and oxidized flavoproteins (Fp including FAD) to probe mitochondrial metabolic states in isolated mitochondria, intact cells and tissues ex vivo/in vivo since the 1950s (Chance and Baltscheffsky 1958; Chance and Jobsis 1959; Chance et al. 1962, 1979; Chance 1966; Chance and Schoener 1966; Hassinen and Chance 1968; Mayevsky and Rogatsky 2007). When excited by UV light (~366 nm), NADH emits fluorescence peaked at ~450 nm. Oxidized flavoproteins have green fluorescence (~525 nm) if excited by blue light (~425 nm). The NAD and reduced flavoproteins do not have such fluorescence signals. These fluorescence signals mainly originate from the mitochondrial compartment (Scholz et al. 1969; Rocheleau et al. 2004; Nichols et al. 2005; Mayevsky and Rogatsky 2007; Blinova et al. 2008), and the indices e.g. NADH, Fp, Fp/NADH, NADH/(NADH+Fp), and Fp/(NADH+Fp) have been shown as sensitive to mitochondrial metabolism and redox state (Chance and Williams 1955a; Chance and Williams 1955b; Chance and Baltscheffsky 1958; Chance and Schoener 1966; Fisher et al. 1976; Chance et al. 1979; Masters et al. 1981; Mayevsky et al. 1983; Kitai et al. 1992; Sato et al. 1995). The ratiometirc quantities reduces their sensitivity to hemodynamic artifacts and mitochondrial densities (Chance et al. 1979; Li et al. 2009a).

To image tissue mitochondrial redox state at a high spatial resolution, redox scanning (Quistorff et al. 1985; Gu et al. 2002; Li et al. 2009a; Xu et al. 2009b) a cryogenic NADH/flavoproteins fluorescence imager was developed by the Chance laboratory to provide 3D maps (resolution $50\times 50\times 20\ \mu m^3$) of mitochondrial redox status by acquiring ex vivo the NADH and Fp fluorescence images of frozen organs/tissues in liquid nitrogen. Its submillimeter spatial resolution is suitable for probing the spatial heterogeneity of the tissue metabolic state. Redox scanning employs snap-freezing procedures to maintain the tissue metabolic state the same as or similar to the in vivo situation. Tissues mounted in a liquid nitrogen chamber are grounded away at various depths to expose surface planes for a flying-spot scanning with a fiberoptic probe. The fluorescence signal acquisition is time-shared between NADH and Fp channels and recorded by a photomultiplier tube (PMT). CCD-based cryogenic redox imager was also developed by replacing the scanning probe and PMT with a cryogenic microscope and CCD detection system (Li et al. 2009a; Ranji et al. 2009; Xu et al. 2009a). The CCD redox imager can acquire redox images of tissues much faster (tens of minutes versus seconds) and a higher spatial resolution (5 μm vs 50 μm) than the redox scanner.

Redox scanning has been extensively employed to study mitochondrial metabolism and redox state in normal tissues and diseases (Barlow et al. 1979; Mayevsky et al. 1983; Haselgrove et al. 1990; Kitai et al. 1992; Sato et al. 1995; Shiino et al. 1999; Ramanujam et al. 2001; Zhang et al. 2004a; Xu et al. 2010; Xu et al. 2011a, b, c). The redox ratio Fp/NADH of freeze-trapped liver mitochondria was shown to correlate with the oxidation-reduction state modulated by the β-hydroxybutyrate/acetoacetate couple (Chance et al. 1979). The Fp/NADH ratio of frozen liver samples from human subjects as measured by NADH-flavoprotein fluorescence imaging correlated linearly with the blood ketone body ratio (acetoacetate/β-hydroxybutyrate) (Ozawa et al. 1992), which might reflect the NAD^+/NADH redox potential coupled via β-hydroxygutyrate dehydrogenase in the mitochondria.

Redox scanning may be applied to biopsy samples snap-frozen right after being removed from the body (Ramanujam et al. 2001; Xu et al. 2012). This diagnostic tool requires only a small tissue sample (~1 mm×1 mm×500 μm) to image. The remaining tissue samples can be further processed with histological assays and correlated with redox images. Another direction of research development is to employ two-photon fluorescence imaging of NADH and Fp (Ramanujan et al. 2005; Skala et al. 2007b) which has a deeper tissue penetration depth than single photon fluorescence and can image the mitochondrial redox state in live tissues. But this approach is still limited by the tissue penetration depth of less than 1 mm. This technique has been used to study the redox state in precancerous tissues in vivo in animal models (Skala et al. 2007a; Levitt et al. 2011) and can be used for deep tissues in patients if coupled with an endoscope or optical biopsy needles (Brown et al. 2009; Zhu et al. 2009).

In summary, the NADH/Fp fluorescence imaging obtains the tissue redox state information which is specific to a mitochondrial compartment and at a high spatial resolution. Although invasive, the redox scanning is the major method currently available for 3D imaging of the mitochondrial redox state in tissue with a wide field of view (~cm) and a submillimeter resolution. A number of other methods (Chung and Jue 1992; Mueller-Klieser and Walenta 1993; Matsumoto et al. 2006; Sattlar et al. 2007; Tisdall et al.

2007; Hyodo et al. 2008; Bohndiek et al. 2011; Keshari et al. 2011; Tachtsidis et al. 2011) may measure tissue redox status but they are limited by lack of specificity for redox couples or mitochondrial compartment or having low spatial resolutions. In recent years genetically-encoded redox-sensitive fluorescence proteins (Dooley et al. 2004; Gutscher et al. 2008; Hung et al. 2011) have been developed so that it is feasible to image the redox state with specificity for redox couples and subcellular compartments at a high spatial resolution. However, these approaches require the genetic transfection of cells with fluorescence proteins and clinical translations would be difficult.

Mitochondrial redox state linked to tumor metastatic potential

Mitochondrial redox imaging using NADH/Fp fluorescences has been extensively used in cancer studies (Drezek et al. 2001; Ramanujam et al. 2001; Zhang et al. 2004b; Li et al. 2007, 2009a; Xu et al. 2010; Liu et al. 2011; Xu et al. 2011b, c). By using the redox scanner we have demonstrated in mouse models that mitochondrial redox imaging indices may potentially provide sensitive biomarkers for tumor metastatic potential. To date we have not found studies other than our own work to probe the connection between mitochondrial redox state of primary tumors and the risk of metastasis or tumor metastatic potential.

We first conducted a redox scanning study on mouse xenografts of five human melanoma cell lines (Li et al. 2007; Li et al. 2009b). These cell lines have been well characterized in vitro and in vivo regarding their aggressiveness. The invasive potentials of these cell lines as measured by the Boyden chamber method fall in the increasing rank order A375P < A375M < A375P10 < A375P5 < C8161. The amount of lung metastases of these cell lines in experimental metastasis mouse models have a rank order A375P < A375P5 < A375P10 < A375M < C8161 (Li et al. 2009a). We implanted these melanoma cells subcutaneously in athymic nude mice and grew tumors within a few weeks. Tumors were then subject to in situ snap-freezing by liquid nitrogen and then excised for redox scanning to obtain multi-slice images at different tissue depths with an in-plane resolution of 80 μm. Significant tissue heterogeneity was identified in these redox images, i.e., NADH, Fp and Fp redox ratio. The aggressive tumors exhibited significant difference between the tumor core and rim, with the cores having higher Fp, low NADH and higher Fp redox ratio. In comparison, the indolent A375P tumors were largely uniform except for sporadic "hot" spots with high Fp redox ratios. We found that the Fp redox ratio could differentiate five human melanoma mouse xenografts spanning a full range of aggressiveness. The more metastatic melanomas exhibited a localized area (the tumor core) with higher Fp redox ratios (more oxidized) than the less metastatic melanomas. A highly significant correlation (R^2=0.97, p=0.002) was obtained between the Fp redox ratios of tumor cores and the invasive potentials of the corresponding cell lines that were measured by the Boyden chamber method. In comparison, the redox ratios averaged over the whole tumor sections have a less significant correlation (R^2=0.63, p=0.1) with the invasive potentials. The redox ratios of the whole-section average can only predict the differences between extremes, i.e., A375P versus other more metastatic xenografts, but not among A375P5, A375P10, A375M and C8161 melanomas (data not published).

We then studied mouse xenografts of two human breast cancer cell lines, the more metastatic MDA-MB-231 line and the less metastatic or indolent MCF-7 line (Xu et al. 2010). Redox scanning has again identified oxidized cores in aggressive tumors and a relatively uniform distribution in the indolent tumors. The redox imaging biomarkers (NADH in the rim, Fp and Fp redox ratio in the core) can readily differentiate between these two types of xenografts with very high statistical significance (p<0.0001). The average redox indices of whole tumor sections do not show statistically significant difference between the two lines, demonstrating the importance of imaging tumor heterogeneity. Furthermore, we have preliminarily observed heterogeneities in mitochondrial redox indices in tumor biopsy samples from breast cancer patients and the redox index differences between cancerous and normal tissues (Xu et al. 2012). The redox index differences between tumor core and rim have also been observed in prostate cancer mouse xenografts as well (Cai et al. 2012).

Note that the more oxidized Fp redox ratio does not necessarily correlate with the high tumor growth rate. In melanoma xenografts of five lines aforementioned, the more invasive ones have faster tumor growth. But the more metastatic MDA-MB-231 breast tumors grow more slowly than the MCF-7 tumors.

Another interesting question is about the metabolic state of cancer cells in the tumor cores. Previously Chance and coworkers (Chance and Williams 1955a; Chance and Williams 1955b; Chance and Baltscheffsky 1958; Chance 1966) have defined 5 metabolic states for mitochondria under different conditions of oxygen, ADP and substrate availability. State 1–4 have adequate oxygen. With low levels of endogeneous substrates and ADP, state 1 represents low levels of oxidative metabolism accompanied by high NADH and low Fp, i.e., low Fp redox ratio. State 2 corresponds to mitochondria starved of substrate but having adequate ADP; this state exhibits low respiratory activity with high levels of Fp and low levels of NADH, i.e., high Fp redox ratio. The State 3 corresponds to adequate levels of substrate and ADP and, hence, high levels of oxidative metabolism. This condition is also indicative of a

high Fp redox ratio, a high Fp but not as high as State 2, and a low NADH but not as low as State 2. State 4, typically a state at rest with adequate supplies of substrate but low ADP, exhibits low mitochondrial respiratory activity with a low Fp redox ratio. State 5 corresponds to anoxic conditions with maximum NADH, lowest Fp redox ratio and minimum (~0) respiration rate. In our melanoma xenograft studies, we found the aggressive melanoma (C8161) had a lower blood perfusion and/or vessel permeability in the tumor core compared to rim or to the indolent melanoma (A375P) based on the measurements of dynamic contrast enhanced MRI (DCE-MRI) in vivo. We also found lower microvasculature patency in the aggressive tumor cores compared to the corresponding rim according to Hoechst dye staining of histological tissue sections. These results indicate a possible substrate starvation (State 2) in the aggressive tumor cores with a high Fp redox ratio.

Although the H&E staining of aggressive tumors often appear morphologically different (more reddish) in the core than in the rim, the tumor cores (not necessarily in the geometrical center) with oxidized redox state may not be regarded as complete necrotic centers for the following several reasons: 1) The tumor regions with comparable high redox ratios were also observed in tumors of small size (4~6 mm in diameter) which are less likely to develop necrotic centers (data not published); 2) MRI of these melanomas and breast tumors seldom showed hyperintensity on T1-weighted images, a feature commonly observed for necrotic tissues (data not published); 3) Another MRI imaging technique sensitive to tissue necrosis, i.e., magnetization transfer MRI indicated viable tissues in some aggressive breast tumor cores with oxidized redox states (data not published); 4) Microscopic observation of melanoma tissue slides stained with DAPI and TUNEL indicated the existence of viable cells with intact nuclei (DAPI) and low apoptosis in those core regions (Xu et al. 2009c); 5) Fluorescence imaging of the pyro-2-deoxy-glucose uptake in MDA-MB-231 tumors indicates heterogeneity in the cores with some areas having high glucose uptake and thus probably not substrate limited (Xu et al. 2011c). The high redox ratio for those regions might indicate high respiratory activities (State 3). Based on all these observations, it is quite possible that the biological states and micro-environment of those cancer cells in the oxidized tumor cores are heterogeneous spatially and temporally. More investigations are needed to understand the significance of these heterogeneities.

The existence of viable cells in the aggressive tumor cores possibly under an inhospitable environment such as starvation led to the hypothesis that those cancer cells may be in the state of autophagy. Autophagy may facilitate the survival of cancer cells under environmental/nutritional stresses and is expected to increase the success rate of metastasis (Lum et al. 2005; Amaravadi et al. 2007). In collaboration with Julian Lum, Ravi Amaravadi and Xiaohong Ma et al., we demonstrated that the more invasive/aggressive melanomas exhibit higher autophagy than the less invasive/aggressive melanoma in 3D cell spheroids and mouse xenografts. Higher autophagy indices predict shorter progression-free survival and overall survival in melanoma patients, and high autophagy activity predicts drug resistance in melanomas (Ma et al. 2011). Further research is needed to investigate the link between mitochondrial redox state, autophagy and tumor metastatic potential.

Significance

Although the underlying mechanism is not clear, our redox scanning studies on cancer mouse models indicate a possibly fundamental connection between mitochondrial redox state and tumor progression to metastasis. Our work also indicates the importance of characterizing the tumor redox state heterogeneity by high resolution imaging methods to predict tumor aggressiveness. It is the redox ratios in the oxidized tumor cores not the whole tumor average that can differentiate better between aggressive and indolent tumors.

With the results across cancer types, we may wonder whether mitochondrial redox potential can be a general mediator in tumor progression to metastasis. As the Warburg effect has been demonstrated as a hallmark in the majority of cancers, further studies about the role of mitochondrial redox state in tumor progression to metastasis might open new pages in cancer research.

On the other hand, redox imaging biomarkers can be useful for clinical cancer management. A major challenge in cancer research is to develop surrogate biomarkers for the risk of tumor metastasis. With ~90 % of cancer patients dying of tumor metastasis, the prognosis of cancer patients is largely determined by the risk of metastasis rather than the tumor size. Compared with other biomarkers that may only provide binary differentiation of malignant from benign lesions, the “scaling” of neoplasia on the basis of the redox imaging indices has an advantage of providing continuously quantitative biomarkers for tumor metastatic potential, which, if successfully established, are expected to facilitate personalized clinical cancer management.

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