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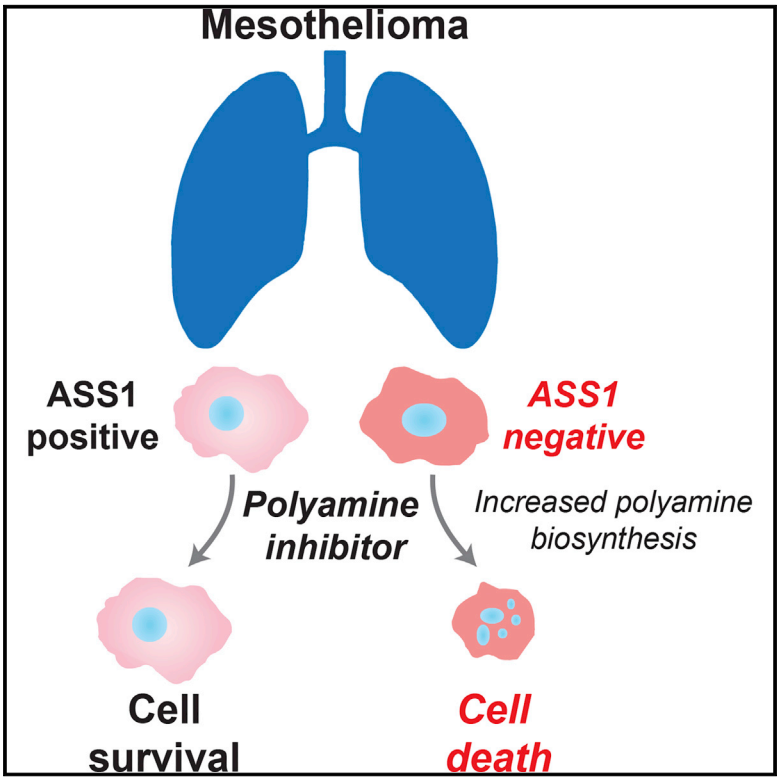
Inhibition of the Polyamine Synthesis Pathway Is Synthetically Lethal with Loss of Argininosuccinate Synthase 1

Graphical Abstract



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In Brief

Locke et al. have generated a model of ADI-PEG20 resistance in mesothelioma cells. They reveal that ASS1-deficient cells have decreased levels of acetylated polyamine metabolites, together with a compensatory increase in expression of polyamine biosynthetic enzymes. This elucidates a synthetic lethal interaction between ASS1 loss and inhibition of polyamine metabolism.

Highlights

- ASS1-deficient tumors become resistant to arginine deprivation via *ASS1* re-expression
- ASS1-deficient cells have decreased levels of acetylated polyamine metabolites
- Polyamine metabolites are decreased in ASS1-deficient cells upon arginine deprivation
- ASS1 deficiency is synthetically lethal with inhibition of polyamine metabolism

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Inhibition of the Polyamine Synthesis Pathway Is Synthetically Lethal with Loss of Argininosuccinate Synthase 1

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SUMMARY

Argininosuccinate synthase 1 (ASS1) is the rate-limiting enzyme for arginine biosynthesis. ASS1 expression is lost in a range of tumor types, including 50% of malignant pleural mesotheliomas. Starving ASS1-deficient cells of arginine with arginine blockers such as ADI-PEG20 can induce selective lethality and has shown great promise in the clinical setting. We have generated a model of ADI-PEG20 resistance in mesothelioma cells. This resistance is mediated through re-expression of ASS1 via demethylation of the *ASS1* promoter. Through coordinated transcriptomic and metabolomic profiling, we have shown that ASS1-deficient cells have decreased levels of acetylated polyamine metabolites, together with a compensatory increase in the expression of polyamine biosynthetic enzymes. Upon arginine deprivation, polyamine metabolites are decreased in the ASS1-deficient cells and in plasma isolated from ASS1-deficient mesothelioma patients. We identify a synthetic lethal dependence between ASS1 deficiency and polyamine metabolism, which could potentially be exploited for the treatment of ASS1-negative cancers.

INTRODUCTION

Cancer cells often rely on subversion of normal metabolic pathways to provide the energy and building blocks for uncontrolled cell division. Such metabolic reprogramming is now appreciated as an enabling hallmark of tumorigenesis and results in the uptake of nutrients for conversion to biomass. It is becoming increasingly appreciated that cancer cells also have altered amino acid metabolism (Tsun and Possemato, 2015). Glutamine, serine, glycine, and arginine have all been implicated in driving cancer cell proliferation (Amelio et al., 2014; Lind, 2004; Wise and Thompson, 2010).

As a versatile amino acid, arginine has connections to a number of metabolic pathways pertinent to tumorigenesis, including nitric oxide, creatine, and polyamine synthesis (Jobgen et al., 2006; Leuzzi et al., 2008). The levels of the rate-limiting enzyme for arginine biosynthesis, argininosuccinate synthase 1 (ASS1), are severely reduced or absent in a number of aggressive and chemoresistant cancers (Delage et al., 2010). The mechanisms behind ASS1 loss are cancer type dependent. For example, in lymphoma (Delage et al., 2012), myxofibrosarcoma (Huang et al., 2013), nasopharyngeal carcinoma (Lan et al., 2014), bladder cancer (Allen et al., 2014), hepatocellular carcinoma (McAlpine et al., 2014), and malignant pleural mesothelioma (MPM; Szlosarek et al., 2006), methylation of the *ASS1* promoter appears to mediate ASS1 repression, whereas in melanoma, the interplay between c-Myc and HIF1α controls ASS1 levels (Tsai et al., 2009). The reason for ASS1 downregulation in tumors is not fully elucidated and renders the cancer cell reliant on, or addicted to, extracellular arginine. Such arginine auxotrophy has been targeted clinically using the pegylated arginine deiminase ADI-PEG20, a mycoplasma-derived protein that degrades arginine to citrulline and ammonia (Ott et al., 2013; Synakiewicz et al., 2014; Szlosarek et al., 2013). Starvation of arginine results in specific cell death of ASS1-deficient cancer cells and provides a means to attack poor outcome and highly proliferative cancers.

Approximately 50% of MPMs do not express ASS1 (Szlosarek et al., 2006), making ADI-PEG20 an attractive personalized therapeutic strategy (Delage et al., 2010) that has shown significant activity in a randomized phase II trial. Encouragingly, this trial has achieved its primary endpoint of a significant improvement in progression free survival (PFS) above the current standard of care (Szlosarek et al., 2013). This is the first biomarker-driven study and first randomized trial in a decade,

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