Functions Related to Drug Persistence

1. Ribosomal Function and Glycolysis/Gluconeogenesis

Ribosomal Function: PROMOTED in persistence

- Ribosome-associated proteins RaiA and Sra show elevated synthesis levels during persistence, suggesting a role in stabilizing inactive ribosomes during dormancy[5].
- During persistence, a fraction of ribosomes is degraded while another is stabilized in an inactive state, which is essential for maintaining the dormant persister phenotype[5].

Glycolysis/Gluconeogenesis: DEPLETED in persistence

- Persister cells typically exhibit reduced glycolytic activity as part of their overall metabolic dormancy[6][7].
- Glycolysis inhibition has been shown to inactivate drug efflux pumps and restore drug sensitivity, indicating that reduced glycolysis is associated with the persister state[6].
- Cancer persister cells have been reported to have diminished "glycolytic reserve," suggesting impaired metabolic plasticity in the persister state[1].

2. Cell Cycle, MAPK Pathway, DNA Replication, and Amino Sugar Metabolism

Cell Cycle and Division: DEPLETED in persistence

- Persister cells are characterized by cell cycle arrest or significantly slowed division, which is a key feature of their drug tolerance[8][9].
- Only a small percentage (approximately 8%) of cell lineages give rise to persisters, with an even smaller fraction (13% of persisters) capable of re-entering the cell cycle during drug treatment[10].

MAPK Pathway: PROMOTED in persistence (with modifications)

- Persister cells escape drug-induced cell-cycle arrest via brief, sporadic ERK pulses generated by transmembrane receptors and growth factors[11].
- The MAPK signaling pathway undergoes rewiring in persisters - from an oncogenic configuration to a receptor-driven configuration that is highly resistant to inhibitors[11][12].

DNA Replication: DEPLETED in persistence

- Persister cells display DNA replication deficits, with significantly reduced DNA synthesis rates compared to non-persister cells[8].
- Inhibition of DNA replication is a key mechanism for persister formation, with proteins like CspD playing important roles in this process[13][14].

Amino Sugar and Nucleotide Sugar Metabolism: DEPLETED in persistence

- While specific data on amino sugar metabolism in persisters is limited, the general reduction in anabolic pathways suggests this function would be depleted[1][7].

3. Sulfur Amino Acids, Phospholipid, and Fatty Acid Metabolism

Sulfur Amino Acids Metabolism: PROMOTED in persistence

- Sulfur metabolism plays a critical role in maintaining redox homeostasis, which is essential for persister survival[15][16].
- Cysteine, a sulfur-containing amino acid, is crucial for glutathione synthesis, which protects persisters from oxidative stress[16][17].

Phospholipid and Glycerophospholipid Metabolism: PROMOTED in persistence

- Persister cells show upregulation of metabolites associated with phospholipids, sphingosines, and phosphatidylcholines[7][18].
- The lipid hydroperoxidase GPX4, which acts on phospholipid hydroperoxides, is essential for persister cell survival[18][19].

Fatty Acid Metabolism and Biosynthesis: PROMOTED in persistence

- Persister cells exhibit a dependency on fatty acid metabolism, particularly fatty acid oxidation[19].
- The fatty acid signaling molecule cis-2-decenoic acid can revert bacterial cells from a tolerant phenotype to a metabolically active state, indicating the importance of fatty acid signaling in persistence regulation[20].

Response to Endoplasmic Reticulum Stress: PROMOTED in persistence

- ER stress response pathways are activated in persister cells as part of their stress adaptation mechanisms[19].
- This response helps persisters manage protein folding stress and maintain cellular integrity during the dormant state[17][19].

4. Amino Acids Metabolism and Nitrogen Utilization

Amino Acids Metabolism and Biosynthesis: PROMOTED in persistence

- Amino acid metabolism is actively maintained in persister cells, with evidence of active amino acid anabolism even in cultures challenged with high drug concentrations[21][22].
- Amino acid starvation can trigger the stringent response via ppGpp, which is a key mediator of persister formation[21][22].

Regulation of Nitrogen Utilization: PROMOTED in persistence

- Nitrogen starvation induces persister cell formation through the NtrC-relA regulatory cascade, which results in ppGpp synthesis[23].
- The regulation of nitrogen utilization is closely linked to amino acid metabolism and the stringent response, both of which are important for persister formation[22][23].

5. Histidine-Purine-Pyrimidine Pathway and Iron Starvation Response

Histidine-Purine-Pyrimidine Superpathway: MIXED effects in persistence

- Purine synthesis is typically DEPLETED in persisters, while pyrimidine synthesis may be PROMOTED depending on the specific conditions[24][25].
- Manipulating purine and pyrimidine synthesis has opposing effects on antibiotic tolerance, suggesting complex roles in persistence[24][25].

Cellular Response to Iron Ion Starvation: PROMOTED in persistence

- Iron starvation response is activated in persister cells, particularly through the iron-responsive protein IRP1[26].
- The iron starvation response contributes to persister formation by altering metabolism and activating stress response pathways[27][26].
- Iron allows cells to acquire a drug-tolerant persister state, and this iron addiction confers a high vulnerability to ferroptosis, a form of regulated cell death[19][26].

6. Cellular Response to Chemical Stress and Pyruvate Metabolism

Cellular Response to Chemical Stress: PROMOTED in persistence

- Stress response pathways, including those responding to chemical stressors, are highly activated in persister cells[14][28].
- These pathways help persisters survive hostile conditions by activating dormancy mechanisms and stress adaptation responses[14][28].

Pyruvate Metabolism: DEPLETED in persistence

- Pyruvate metabolism through the TCA cycle is typically reduced in persister cells[29][28].
- Alternative pathways for pyruvate utilization, such as acetoin synthesis, may be promoted to reduce reactive oxygen species formation and enhance persister survival[28].

7. Proteasome

Proteasome Function: PROMOTED in persistence

- Proteasome activity is important for persister formation, particularly through the degradation of antitoxins in toxin-antitoxin systems[30][14].
- Lon protease, which degrades labile antitoxins, has been shown to be necessary for persister cell formation[14].

8. Cellular Respiration, Oxidative Phosphorylation, and TCA Cycle

Cellular Respiration: DEPLETED in persistence

- Persister cells typically show reduced respiratory activity as part of their dormant metabolic state[29][31].
- Inhibition of stationary phase respiration impairs persister formation, indicating that controlled reduction of respiration is important for persistence[31].

Oxidative Phosphorylation: PROMOTED in persistence (with modifications)

- Recent reports indicate that persisters rely more heavily on oxidative phosphorylation (OXPHOS) and are more sensitive to OXPHOS inhibitors[1].
- This suggests a shift toward OXPHOS-dependent metabolism in persister cells, despite their overall reduced metabolic activity[1][29].

TCA Cycle: DEPLETED in persistence

- Inactivation of TCA cycle enhances persister cell formation, as demonstrated in studies with *Staphylococcus aureus*[29][32].
- Mutations in TCA cycle enzymes like succinate dehydrogenase lead to increased persister formation, suggesting that reduced TCA cycle activity promotes persistence[29][32].

9. Starch and Sucrose Metabolism / Meiosis

Starch and Sucrose Metabolism: Limited evidence for direct relationship with persistence

- While specific data on starch and sucrose metabolism in persisters is limited, general carbohydrate metabolism is typically reduced in persister cells[21][22].

Meiosis: Not directly related to bacterial persistence

- Meiosis is primarily relevant to eukaryotic cells and has limited direct evidence linking it to persister formation in the literature reviewed[2][3].

10. Pentose Phosphate Pathway

Pentose Phosphate Pathway: PROMOTED in persistence

- The pentose phosphate pathway (PPP) shows alterations in persister cells, with evidence suggesting its importance in managing oxidative stress[33][34].
- PPP is crucial for generating NADPH, which is essential for maintaining redox balance and supporting antioxidant systems that protect persisters from oxidative damage[33][34].

Conclusion

Persister cells exhibit a complex metabolic and cellular state characterized by specific adaptations that enable drug tolerance. Key promoted functions include ribosomal stabilization mechanisms, stress response pathways, phospholipid metabolism, and oxidative stress management systems[1][2][4]. Conversely, depleted functions typically include glycolysis, DNA replication, cell division, and TCA cycle activity[8][29][31]. Understanding these metabolic shifts provides valuable insights for developing strategies to target persister cells and overcome drug tolerance in both infectious diseases and cancer[3][4][19].

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