Identifying Metabolic Inhibitors to Target Aggressive Cancers with Deregulated p27kip1

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P27kip1 (p27) is a tumor suppressor protein that is often deregulated in aggressive cancers. Recent evidence from the Sheaff lab suggests p27 deregulation provides a growth advantage by allowing cancer cells to metabolize amino acids when glucose levels are low. If this metabolic switch could be specifically targeted, it might be possible to stop growth of aggressive tumors. Non-Primary Mouse Fibroblast Cells with (p27+/+) and without p27 expression (p27-/-) were used as a model system. When these cells were treated with the glucose analog 2-deoxyglucose (2DG), only those lacking p27 switched to amino acid metabolism. The p27-/- cells could now be specifically killed with rotenone, which inhibits amino acids utilization. Unfortunately, rotenone is highly poisonous and would not be viable as a drug. The objective of this study was to locate a replacement for rotenone. Cells with and without p27 were treated with 2DG and various compounds to identify synergy (ie drugs working together to specifically target p27-/- cells). After evaluating numerous compounds, the amino acid L-phenylalanine was identified as a prospect. When paired with 2-deoxyglucose, L-phenylalanine showed an ability to specifically inhibit metabolism (ATP production) in p27-/- cells, similar to rotenone. Thus, L-phenylalanine is a possible substitute for rotenone that can be used in conjunction with 2DG to specifically target cells lacking p27.

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