The Hormone KL1: A Regulator of Breast Cancer Cell Metabolism

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Background: Klotho is a transmembrane protein that can be shed and can act as a circulating hormone in three forms: soluble klotho (KL1 + KL2), KL1, and KL2. Klotho was discovered as a gene implicated in aging through inhibition of the IGF-I pathway. Our laboratory discovered the role of klotho as a tumor suppressor in breast cancer and other malignancies. Furthermore, we showed that the KL1 domain mediates this activity. Altered cancer cell metabolism is a hallmark of cancer and our lab demonstrated various effects of klotho on breast cancer cell metabolism. Thus, klotho inhibited glycolysis and activated adenosine monophosphate activating kinase (AMPK), an energy sensor pathway. Moreover, inhibition of AMPK reduced the tumor suppressor activity of klotho.

Objectives: To assess the effect of KL1 on breast tumor cells metabolism, as KL1 possesses the tumor suppressor activity of klotho.

Methods: We used MCF-7 breast cancer cells treated with soluble or over-expressed KL1 and klotho. Glycolysis was assessed by measuring mRNA levels of key glycolytic enzymes using reverse transcription polymerase chain reaction and by measuring lactate and glucose levels in media. The AMPK pathway was studied by monitoring AMPK phosphorylation as well as its down-stream target, acetyl-CoA carboxylase, using western blotting. Wound healing assay was used to assess cell migration.

Results: KL1 treatment reduced glycolytic enzymes mRNA levels and the activity of hexokinase, similar to klotho treatment. Furthermore, KL1 reduced glucose uptake and decreased lactate production. KL1 elevated phosphorylated acetyl-CoA carboxylase and phosphorylatedAMPK levels. Inhibition AMPK (using a mutant AMPK activator) stopped KL1 from inhibiting cell migration, suggesting AMPK underlies klotho's tumor suppressor activity.

Conclusions: Our data indicate KL1 as a regulator of metabolic activity in breast cancer and suggest that metabolic alterations underlie KL1 tumor suppressor activities. Furthermore, as KL1 and klotho share a similar effect on cell metabolism, our results further support the central role KL1 domain plays in klotho's tumor suppressor activity.

Capsule

Vitamin A as an antimicrobial for skin infections

Vitamin A is an essential fat-soluble micronutrient that regulates immune function through its derivative, retinoic acid. One role of retinoic acid is to control skin infection and inflammation. **Harris** and colleagues reported that dietary vitamin A regulates the expression of the antimicrobial protein RELMα in the skin. RELMα, which is induced by the skin microbiota, can kill bacteria by disrupting their membranes. Mice lacking RELMα have an altered skin microbiota composition and an enhanced susceptibility to certain bacterial infections. The study showed how vitamin A effectively treats skin conditions such as acne and psoriasis.

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Capsule

Broadening targeted therapy in cystic fibrosis

There are more than 1700 mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene that cause cystic fibrosis. Some mutations occur frequently, whereas others affect very few or individual patients. Modulators have been developed to target specific CFTR mutations classified according to their functional impact on the encoded protein. In a perspective, **Manfredi** and colleagues discussed the emerging view that many CFTR mutations have pleiotropic effects and so more patients could benefit from modulator therapy but do not receive it. Moreover, individuals with ultrarare CFTR mutations are often do not receive these targeted drugs. The authors outlined the approaches needed to broaden the personalization of these modulators to treat more patients.

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"Understanding is a two-way street"

Eleanor Roosevelt (1884–1962), American political figure, diplomat, and activist, served as first lady of the United States during her husband's four terms as president