Dna Damage Increases Functional Differentiation Of Mammary Gland Alveolar Cells During Lactation

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BACKGROUND

Endoreplication is the process by which a cell undergoes DNA replication in the absence of cell division, becoming polyploid. Developmentally programmed endoreplication occurs in several mammalian tissues during pregnancy and is usually linked to terminal differentiation. In the placenta, trophectoderm cells undergo endoreplication and differentiate into trophoblast giant cells, which penetrate the uterus and promote blastocyst implantation. Subsequently, in the uterus, stromal cells of the endometrium endoreplicate and differentiate into decidual cells, which further facilitate blastocyst implantation and vascularization. Another example is pregnancyinduced
liver growth occurring through hepatocyte hypertrophy that is generated by endoreplication.
In the mammary gland (MG), alveolar cells undergo endoreplication at the onset of lactation. While these phenomena have long been observed and considered adaptations necessary for tissue expansion during pregnancy, the molecular mechanisms driving these pregnancy-induced endoreplication events remain poorly understood.

The MG plays an essential role in the survival of mammalian species by producing milk required for the nourishment of offspring. During pregnancy, the MG undergoes a profound morphological change known as alveologenesis, in which epithelial luminal progenitors proliferate and subsequently differentiate into polyploid alveolar cells that secrete milk during lactation. This polyploidization of the MG is conserved across many mammalian species, including mice and humans, and it is required for efficient milk production. Once breastfeeding is complete, in a process known as involution, massive cell death clears these milk-producing polyploid cells and tissue remodeling brings the epithelium back to a pre-pregnancy-like state.
The mechanisms regulating the transition from a proliferative mitotic cell cycle to an endocycle in the MG have yet to be elucidated. The DNA damage response (DDR) plays a central role in the regulation of the cell cycle, to ensure genomic stability and safeguard inheritance. In the event of DNA damage, the DDR kinases ATM and ATR initiate a signaling cascade that activates cell cycle checkpoints, at either the G1/S or G2/M transitions, through inactivation of CDK/Cyclin complexes. These checkpoints permit the DDR to perform any necessary repairs before giving rise to a daughter cell. DNA damage as a consequence of exogenous genotoxic insults has been shown to trigger endoreplication and terminal differentiation

CONTACT

Jeff M. Jackson
jjackso6@ucsc.edu
tel: .

INVENTORS

- Hinck, Lindsay E.

OTHER INFORMATION

KEYWORDS

Milk, Lactation, bovine, CDK1, DNA damage, increased milk production, cdk1 inhibitor

CATEGORIZED AS

- **Agriculture & Animal Science**
  - Animal Science
- **Veterinary**
  - Large Animal
  - Therapeutics

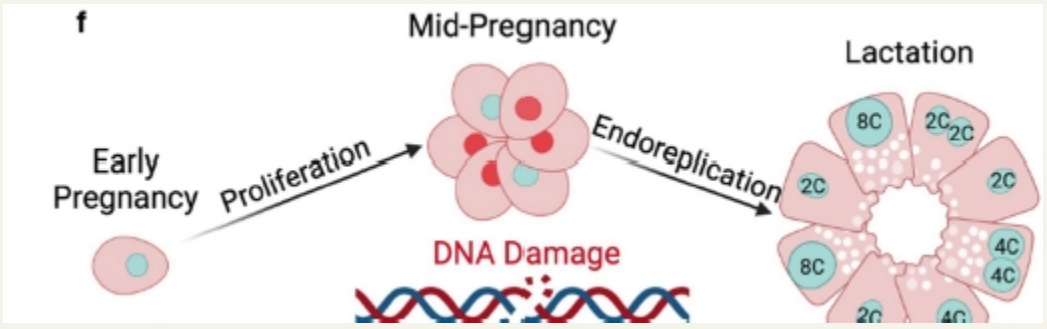
RELATED CASES

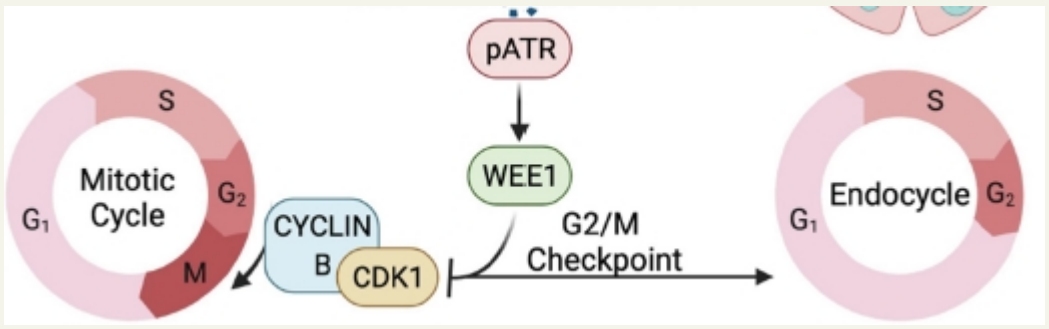
2023-910-0

through G2/M checkpoint activation .

TECHNOLOGY DESCRIPTION

Administration of a CDK1 inhibitor, particularly one that targets mammary gland alveolar cells, to a lactating mammalian subject increases milk production. CDK1 inhibitors include DNA damaging agents.





Cartoon representing the regulation of alveolar endoreplication by the ATR-DNA damage response pathway. Proliferation of alveolar cells results in accumulation of DNA damage during pregnancy and activation of the ATR pathway. As a result, ATR mediates the transition from a mitotic cell cycle into an endocycle through the activation of the CDK1 inhibitor WEE1, which activates the G2/M checkpoint and regulates alveolar endoreplication during lactation.

Physiological DNA damage accumulates during the extensive cell proliferation of mid-pregnancy and drives endoreplication and terminal differentiation through G2/M checkpoint activation at the onset of lactation. This mechanism involves the activation of the ATR-mediated DDR to replication stress, and the subsequent activation of the G2/M checkpoint. WEE1 governs this process, revealing a novel role for this CDK1 inhibitor in the regulation of mammalian endoreplication.

The CDK1 inhibitor can work through a number of different mechanisms:

It can increase the expression of the Wee1 like protein Kinase or it can be a DNA damanging agent, such as a DNA intercalating agent like an anthracyline such as doxorubicin. The DNA damaging reagent can be an inhibitor of ribonucleoside diphosphate reductase such as hydroxyurea. It can also be an inhibitor of CDK1 such as a CDK1 antisense mRNA or other inhibitory mRNA like an siRNA or miRNA.

APPLICATIONS

- Increasing milk production in a bovine, ovine, caprine, or camelid.
- Increasing milk, production in a lactating human.

ADVANTAGES

Increases milk production without the use of growth hormones.

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
United States Of America	Published Application	20240374626	11/14/2024	2023-910

Additional Patent Pending

RELATED MATERIALS

- Physiological DNA damage promotes functional endoreplication of mammary gland alveolar cells during lactation - 04/17/2024

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Compositions and Methods Useful in Promoting Milk Production

University of California, Santa Cruz
Industry Alliances & Technology Commercialization
Kerr 413 / IATC,
Santa Cruz,CA 95064

Tel: 831.459.5415
innovation@ucsc.edu
https://officeofresearch.ucsc.edu/
Fax: 831.459.1658