REVIEW ARTICLE

CRISPR Technology in Chalcone Derivatives: Innovations in Biosynthetic Pathways and Therapeutic Potential

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ABSTRACT
Clustered regularly interspaced short palindromic repeats technology has revolutionised genetic engineering along with its efficiency and precision. It shows targeted modification of DNA sequences allowing the changes of activation suppression and alteration of specific genes. As the chalcone derivatives CRISPR play an important role in increasing biosynthesis by precisely genes involved in the phenylpropanoid pathway, what are chalcone synthase. The modification involved in the genetic intervention boosts the yield of chalcone and enhance the creation of novel drugs with improved therapeutic property such as anti-cancer, anti-inflammatory and anti-microbial effects. CRISPR technology based studies give profound knowledge into the genetic network and regulatory mechanism by governing chalcone production. These pathway unrevelling the CRISPR aids in optimising biosynthetic root in plants and microorganism, paving the innovative drug discovery and way for scalable production.
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INTRODUCTION

Chalcones are naturally occurring flavonoid compound use for their broad spectrum and biological activities including such as anti inflammatory antimicrobial antioxidant and anticancer properties. The potential of therapeutic leads to increasing the interest in the modification optimization and production for pharmaceutical applications industry. Although the challenge is remain in efficiently production of chalcones and modifying the structure to enhance their biological activity.[1] For this the advanced tool such as CRISPR technology become the essential for the research of chalcones.

Challenges in the Biosynthesis of Chalcon

The biosynthesis process of chalcones in plant is a complex process that involve multiple enzymatic reactions within the phenylpropanoid pathway which mainly include chalcone synthase, chalcone isomerase. The production of chalcones can be influenced by the many factors which include genetic variation availability of precursors and environmental conditions. Metabolic engineering and traditional breeding techniques has been limited success in significantly increasing the yield of chalcones with improved therapeutic activity.

Precision and targeted gene editing

the advantages of the CRISPR technology is its ability to locate the specific genome to make a precise modification. It can be used to edit and target genes for involvement in the phenylpropanoid pathway to increase the chalcone production. The precision of these will reduce the need for labour intensive and less efficient traditional breeding method. For these CRISHPR can be used to up regulate the specific enzyme and knockout negative regulators. It can also be used to integrate foreign biosynthetic genes into the genome and allowing the production of chalcones with different structure or properties that are not naturally occurring.

Tailoring Chalcones for specific Therapeutics Applications

The technology of CRISPR allows 2 change the genetic pathway involved in the biosynthesis of chalcones to produce novel derivatives with increase in the property. That can be implemented in several pathway like modification of structural pharmacokinetic enhancing and targeting specific diseases.

Overcoming Limitation of Traditional Methods

the method used for traditional are chemical synthesis plant cultivation for chalcogens production microbial fermentation are often faces several challenges such as low yield, purification process get complex and high production cost. CRISPR technology offers a more scalable alternative for optimising the production and efficient. This can also be used to create high yield, enhancing the stress tolerance and reduce the variability.

CRISPR in Synthetic Biology and Metabolic Engineering

The utilization of CRISPR in the biosynthetic and metabolic engineering can further advance the chalcone research by allowing the construction of new metabolic

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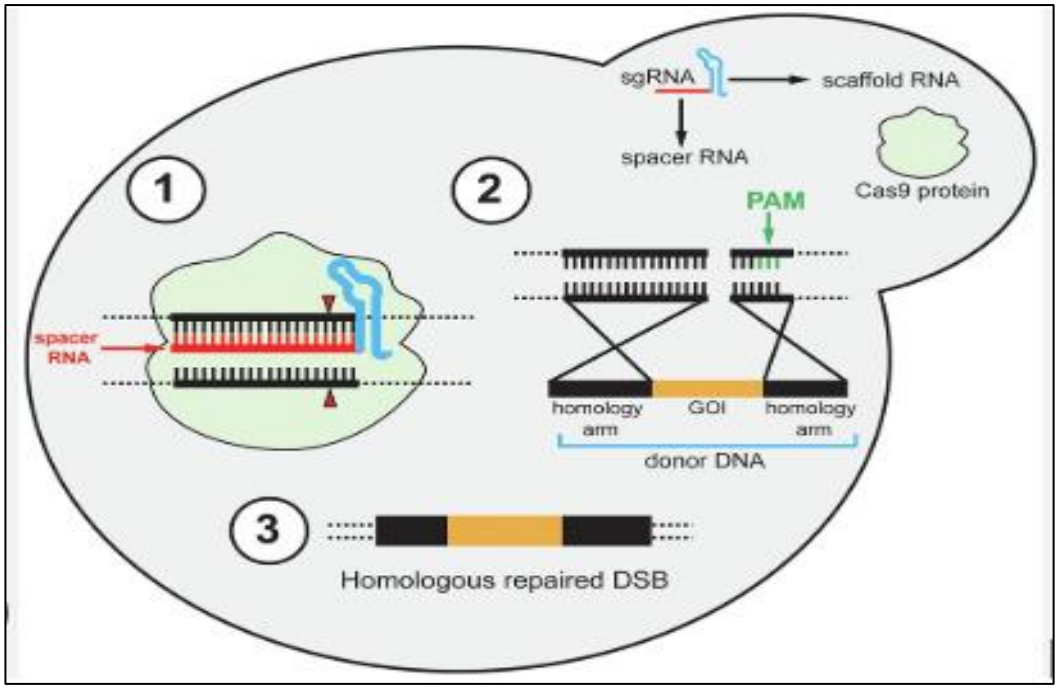

Figure 1: Sequences of CRISPR

pathway for the synthesis of chalcones. Cris PR integrating with biological system it approaches researcher can modify design more efficient biosynthetic route for chalcones production and allowing the novel derivatives for creation with improved or tailored bioactivity.

Increased Understanding of Chalcone Biosynthetic Pathways

CRISPR also allow valuable insight into the genetic pathway that holds chalcone biosynthesis. By knocking out the specific gene over expressing the researcher can elucidate the role of various enzymes and regulatory factor in the production of chalcones dead improve and increase chalcones yield and bioactivity.[2,3]

CRISPR Technology

CRISPR is a groundbreaking technology for gene editing that enables form the precise changes or modification to the DNA of living organisms. Originally it is discovered as a part of immune system in bacteria it is also used in the research of genetic and therapeutic applications. It allows to target specific genes by using molecular tool named CRISPR-Cas9.[4]

Key Components of CRISPR

Sequences of CRISPR:

Short repeated DNA sequences found in the bacteria genome which store snippets of DNA viral that have previously attacked the bacteria.

Cas9 Protein: This enzyme act like a molecular scissor and enables to cut DNA at a specific site and allowing the deletion insertion or modification of genetic material.

Mechanism of Action:

Guide RNA(g RNA): RNA synthetic molecule that is designed to match the target DNA sequences it guide the ca as 9 protein to the precise location in the genome.

DNA Cleavage: Cas9 Protien, allow the gRNA make a break in the double strand of DNA at the target site.[5]

DNA repair: The DNA cut the cell attempt to repairs. The repair process is harness to introduce the genetic changes either by using the cell's natural mechanism of repair to insert the DNA new or by forming error during the repair to knockout a genes. (non homologous end joining).[6]

Variants and Advancements in CRISPR Technology:

CRISPRa (CRISPR Activation)

CRISPR is a technique design to activate the expression of a specific gene without making permanent change to the DNA sequence. This is mainly useful for studying the gene function by increasing the target gene expression to observe it effects.[7] CRISPRa uses a dead Cas9 protein that is inactive catalytically (unable to cut the DNA). dCas9 is fused with the transcriptional activators (such as VP64 OR p300), that recruit the cells transcriptions machinery to the targeted gene's promoter region. The target gene get increased its expression by activation it.

Applications:

Gene activation: to show the effects of ever expressing a gene.

Disease models: It is used to activate gene involved in disease to understand there role in disease progression.

Synthetic Biology: used in synthetic biology to design new gene networks or enhance the expression of beneficial genes.[8]

CRISPRi (CRISPR Interference)

CRISPRi is a counterpart to the CRISPRa, here the target is to silence or interfere with gene expression. This also useful in studying gene function by repressing specific gene without altering the DNA sequences. As similar to CRISPRa, CRISPRi uses a dead Cas9 (dCas9) protein, instead of transcriptional activators, dCas9 is fused with repressors (KRAB). The dCas9 protein binds to the promoter region of the target gene, blocking transcription and effectively silence the gene.[9]

Applications:

Gene knockdown: To study the effect of gene silencing, especially for genes that are essential or have complex functions.
Functional genomics: CRISPRi enables systematics, reversible silencing of genes in various organisms to find out gene involved in particlue pathways or diseases.
Therapeutic Research: Targeting genes for silencing to treat disease caused by overactive genes, such as certain cancers or genetic disorders.

Base Editing

Base editing is an advanced form of CRISPR technology that allows precise conversation of one DNA base pair into another without causing double stranded break in the DNA. This greatly improves the efficiency and accuracy of gene editing particularly for point mutation (single base changes). Base editors are fusion routines that combine a dead Cas9 with a base modified enzyme. The dCas9 proteins by guide the editor to the target sequences and the base modifying enzyme catalyse the conversion of one ways to another. This allow for very precise edit and the nucleotide level without pausing break into double stranded DNA.[10]
Applications:
Point mutation correction: ideal for correcting point mutation that is responsible for genetic disease like sickle cell anemia and cystic fibrosis.
Enhanced precision: bees editing reduces the risk of off-target effects for large insertion deletion that can occur with traditional CRISPR Cas9.
Gene function studies: allows for creation of point mutations in a gene to study its functional role.

Prime Editing

Prime editing is even more recent and revolutionary advancement in CRISPR technology. It is often referred to as "CRISPR 3.0" due to its unparalleled precision and ability to make more complex genetic changes including insertion, deletion, and point mutation. Prime editing utilise of prime editor which consists of dCas9 nickase fused with reverse transcriptase enzyme. The rivers transcriptase enzyme use of brain editing guide RNA that provide both the target sequence and the desire genetic changes. The enzyme right to new sequences directly into the DNA, replacing the old sequences with the desired edit. Unlike traditional CRISPR Cas9 which relies on the cell repair mechanism to introduce edits, prime editing directly inserts the new sequence without relying on error front prepare pathways.[11]
Applications:
Precise and complex edits: prime editing can make more complex genetic changes with greater accuracy search as inserting a gene or correcting multiple mutations.
Gene therapy: it has the potential to correct wide range of genetic disorder including those caused by larger genetic mutations example Duchenne muscular dystrophy, beta thalassemia.
Precision medicine: prime editing allowed for the precise correction of genetic mutations in a patient cell offering potential cures for previously untreatable genetic diseases.

Advantages of CRISPR over Traditional Genetic Tools

CRISPR technology has revolutionised genetic engineering by providing a more precise, efficient and versatile method for editing gene compared to traditional genetic tools.[12,13]

Precision and Specificity

CRISPR-Cas9 allows for highly specific targeting of a particular gene or genetic sequence within the genome. This precision is achieved using guide RNA that directs the Cas9 enzyme to the exact location of the DNA to be edited. In similar order method like Zinc Finger Nuclease(ZFNs) or Transcription Activator Like Effector Nucleases (TALENs) were more complex and less precise.
CRISPR's allow for programming to target specific sequences significantly reduce of target effects compared to other gene editing tools, which can lead to unintended changes elsewhere in the genome.

Efficiency and Speed

CRISPR is much quick than other traditional genetic tools. Traditional methods opened required weeks to months for the design and execution of genetic editing, while CRISPR can modify gene within days.
CRISPR has higher editing efficiency than older method like ZFN and TALENs reducing the need for multiple attempts. This make it a more reliable tool for large scale genetic modifications.

Simplicity of CRISPR's Design and Implementation

CRISPR simpilicity is one of the simplest and its greatest strengths. The main components Cas9 protein and guide RNA on more easier to design and implement compared to ZFN and TALENs. With CRISPR the only required step is to design a guide RNA to match the target sequence. It can be used to edit multiple genes simultaneously which is more challenging with other gene editing technology.

Versatility in Different organisms

CRISPR technology is versatile and can be used in a wide variety of organisms including bacteria plants animals and humans are contrast with older tool like ZFN and TALENs. CRISPR has enabled gene editing in a non model Organism that work previously difficult or impossible to edit expanding the scope of genetic research and applications.[14]

Cost effectiveness

The components needed for Cris PR based gene editing are inexpensive compare to older technology like ZFNs and TALENs which required custom design protein that are very costly to produce. The simplicity and low cost of CRISPR make it ideal for large scale applications such as drug discovery or agriculture biotechnology.

Flexibility in Editing

CRISPR technology has evolved to allow not only gene editing but gene activation or gene silencing without changing the underlying DNA sequence. This flexibility is particularly useful for functional genomics study.
Advancement such as bees editing and prime editing allow for precise single nucleotide changes or complex editing without the need of double strand break offering a much higher level of accuracy than traditional methods.

Application in gene therapy

CRISPR is widely used as a promising tool for gene therapy particularly for correcting genetic mutation that causes

diseases. Traditional methods lag the precision and efficiency needed for gene correction at the level required for therapeutic application.

CRISPR has soon threat promise in editing the genes of human cell potentially allowing for the treatment of genetic please order like sequel cell anemia, muscular dystrophy and cystic fibrosis.

Broad Application in Various Fields

CRISPR has transformed agriculture biotechnology by enabling the development of genetically modified crops with improved traits such as resistance to disease drought tolerance and enhanced nutritional content. Traditional method for creating genetically modified Organism for more time consuming less precise and often face public resistance.

In synthetic biology CRISPR has allowed for the creation of genetic as biotechnology and pharmaceutical engineered microorganism with specific function such as the production of biofuels or pharmaceuticals. The ability to provide gene rapidly and the seriously has expanded the potential of synthetic biology in industry such as pharmaceutical and biotechnology.[15]

Ethical Considerations and Safety

CRISPR allows for more control reversible and less invasive genetic modification compared to previous methods. This has lead to different confidence in using CRISPR for therapeutic purpose with the possibility of target temporary modification in patients genome.

While target effect are still of concern CRISPR technology has evolved with improve method to reduce this risk make it safe for for clinical and therapeutic application compared to older genetic tools.[16]

Chalcone Biosynthesis: The Genetic Landscape

They are synthesis through the phenylpropanoic pathway a key metabolic route that produce a variety of secondary metabolites include flavonoids, lignins and anthocyanins understanding the genetic landscape of chalcone biosynthesis is essential for iemproving the production of chalcone and their derivatives particularly for therapeutic purposes.

Phenylpropanoid Pathway

The phenylpropanoid pathway is a major biosynthetic root in plants that starts with amino acid phenyl alanine and leads to the production of various phenolic compounds including chalcones. The pathway includes several enzymatic steps beginning with conversation of phenylalanine into cinnamic acid and proceeding through as series of reaction that generate flavonoids and other metabolites.

Here is simplified overview of the phenylpropanoid pathway which ultimately leads to chalcone production:

Phenylalanine → Cinnamic acid → p-Coumaric acid → Cinnamoyl-CoA → Chalcone

This pathway involves the crucial enzyme chalcone synthesis, which catalyzes the formation of chalcones, a class of flavonoid precursors.[17]

Key Enzymes Involved in Chalcone Biosynthesis

The biosynthesis of chalcones involves several important enzyme. This enzymes are encouraged by jeans that are tightly regulated and can be manipulated to enhance Chalcone production. There are the key enzymes involved in this pathway like Phenylalanine Ammonia-Lyase (PAL), Cinnamate-4-Hydroxylase (C4H), 4-Coumarate-CoA Ligase (4CL), Chalcone Synthase (CHS),Chalcone Isomerase (CHI).

Genetic Regulation of Chalcone Biosynthesis

The production of chalcones is tightly controlled at the transcriptional level by several key transcription factors. These transcription factors regulate the expression of enzymes involved in the phenylpropanoid pathway. Some of the important regulatory factors include MYB Transcription Factors, bHLH Transcription Factors and WD40 Proteins. MYB family proteins are regulate the expression of genes encoding enzymes like CHS, CHI, and other flavonoid biosynthetic genes. MYB11, MYB12, and MYB111 are known to regulate the expression of chalcone synthase in plants. Basic Helix-Loop-Helix (bHLH) transcription factors also play a significant role in regulating flavonoid biosynthesis by interacting with MYB transcription factors. WD40 proteins help stabilize and enhance the function of MYB-bHLH complexes.[18]

Chalcone Biosynthesis Pathway and its Role in Plant Metabolism

Chalcones are intermediates in the flavonoid biosynthesis pathway, which is essential for plant defense, pigmentation, and growth. Flavonoids, derived from chalcones, play a variety of roles in plant biology, including UV Protection, Antioxidant Activity, Pollinator and Attraction Disease Resistance

Engineering Chalcone Production: Role of CRISPR Technology

The precise regulation of chalcone biosynthesis holds great promise for enhancing the production of chalcones and their derivatives for therapeutic and industrial applications. CRISPR technology can be employed to manipulate the genes involved in the phenylpropanoid pathway, particularly CHS and other enzymes like PAL, C4H, and 4CL, to boost chalcone production in plants.

Gene Knockouts: CRISPR can be used to knock out genes encoding enzymes that lead to unwanted by-products in the pathway, thus channeling more precursors into chalcone synthesis.

Gene Overexpression: By overexpressing key genes like CHS, the production of chalcones can be enhanced in plants.

Pathway Redirection: CRISPR allows for the creation of synthetic biosynthetic pathways to increase the production of chalcones by introducing or modifying regulatory genes and enzymes in the phenylpropanoid pathway.[19]

Applications of CRISPR in Chalcone Derivatives

The advent of CRISPR technology offers significant opportunities to enhance the production of chalcones and their derivatives through precise genetic modifications. Below are some key applications of CRISPR in the context of chalcone derivatives:

Enhancement of Chalcone Biosynthesis

CRISPR can be used to Overexpress or Knock-In Target Genes: By overexpressing CHS or other genes involved in the phenylpropanoid pathway, CRISPR can increase the flux of metabolites towards chalcone production.

CRISPR can also be used to knockout or reduce the expression of genes that lead to the production of by-products or unwanted metabolites in the biosynthesis of chalcones.

Manipulation of Transcriptional Regulators:

CRISPR can be employed to manipulate transcription factors that regulate the expression of CHS and other flavonoid biosynthetic genes. The manipulation of these regulators can also improve the adaptability of plants to different environmental conditions, increasing chalcone yield under stress conditions (e.g., UV light exposure, pathogen attack).[20]

Customizing Chalcone Derivatives for Specific Therapeutic Applications

Chalcones exhibit a wide range of biological activities, but their activity is often modulated by small changes in their chemical structure. CRISPR can facilitate the biosynthesis of modified chalcone derivatives by introducing specific modifications into the biosynthetic pathway. This can be done in the following ways:

Enzyme Engineering for Derivative Production:

Using CRISPR/Cas9 to modify the expression of specific enzymes involved in chalcone modification can lead to the production of chalcone derivatives with improved or novel bioactivities. For instance: C-glycosylation or O-methylation of chalcones can be enhanced by regulating the activity of the enzymes responsible for these modifications, creating derivatives with better solubility, stability, and bioactivity.

Modifying genes responsible for the formation of isochalcones or dihydrochalcones could yield derivatives with specific anticancer, antimicrobial, or anti-inflammatory activities.[21]

Enhancing Stress Tolerance and Metabolite Accumulation

Chalcone biosynthesis in plants is often induced by stress factors such as UV radiation, pathogen attack, or nutrient deficiencies. CRISPR can be used to enhance plants' stress tolerance and increase chalcone production under challenging environmental conditions.

Stress-Induced Production of Chalcones:

By targeting the transcription factors that respond to environmental stress (e.g., MYB11, MYB12), CRISPR can increase the expression of chalcone biosynthesis genes during stress conditions, leading to higher yields of chalcones and their derivatives.

Given that chalcones help plants cope with UV stress by acting as UV filters, CRISPR can be used to enhance the plants' natural UV response, thereby increasing the production of chalcones in response to UV exposure.

Improving the Efficiency of Chalcone Production in Microbial Systems

Microbial biosynthesis offers a more controlled and efficient system for large-scale production of chalcones and their derivatives. CRISPR can be used to engineer microbial hosts (e.g., yeast, bacteria) for the efficient production of chalcones.

CRISPR can be employed to introduce or optimize the phenylpropanoid pathway in microorganisms. This could involve Incorporating plant-derived genes (e.g., CHS, PAL) into microbial genomes to enable microbial systems to produce chalcones. Optimizing the production process by engineering regulatory networks in microbes to maximize the conversion of sugars or other substrates into chalcones.

Agricultural Applications for Enhanced Chalcone Yield

CRISPR can be used to develop crops that produce higher yields of chalcones, either for their therapeutic properties or for their use in food and cosmetic industries.

Overexpression of CHS or genes involved in the phenylpropanoid pathway could increase the production of chalcones in medicinal plants or crops, improving their commercial value.

CRISPR could be used to create crops that not only produce more chalcones but also have improved resilience to environmental stresses (e.g., drought, pests, UV light), making them more sustainable for large-scale cultivation.[22]

Enhancing Bioavailability and Pharmacokinetics of Chalcone Derivatives

The therapeutic efficacy of chalcones can be limited by their poor bioavailability, rapid metabolism, and poor absorption in the gastrointestinal tract. Their lipophilic nature, low solubility, and high first-pass metabolism often reduce their effectiveness when administered orally. [23] These issues can be addressed through the following CRISPR-based strategies:

CRISPR can be used to alter chalcone derivatives to improve their solubility and bioavailability. For example, the introduction of hydrophilic groups (such as hydroxyl, amino, or carboxyl groups) can be engineered into chalcone structures via CRISPR editing of the genes responsible for their biosynthesis.

By editing genes involved in the phase I and phase II metabolic pathways, CRISPR could help create chalcone derivatives that are less susceptible to metabolic degradation. This could extend the half-life of chalcones in the body and increase their therapeutic window.

The bioavailability of chalcones can be limited by efflux transporters such as P-glycoprotein that pump drugs out of cells, reducing their therapeutic effect. CRISPR can be used to knockdown or knockout genes encoding these transporters, thus allowing higher intracellular accumulation of chalcone derivatives.

CRISPR can also be used to engineer cells to produce nanocarriers such as liposomes or micelles for more efficient drug delivery. By modifying the surface properties of these nanocarriers to target specific tissues or organs (e.g., tumors), CRISPR can facilitate targeted delivery of chalcones, improving their pharmacokinetics and reducing side effects.[24]

Modifying Chalcone Structures to Target Specific Diseases

CRISPR technology allows researchers to directly edit metabolic pathways to produce chalcone derivatives with properties tailored for specific diseases.

Chalcones have shown promise as anticancer agents by inducing cell cycle arrest, apoptosis, and inhibiting metastasis. Using CRISPR, chalcone structures can be modified to improve their specificity for cancer cells.

CRISPR could help enhance the expression of chalcones that target cancer-specific pathways, such as those involved in cell signaling, angiogenesis, and DNA repair mechanisms.

Chalcones can be engineered to promote apoptosis in cancer cells more efficiently by modifying their structures to activate pro-apoptotic proteins or inhibit anti-apoptotic pathways.

CRISPR can be used to modify chalcones to target specific biochemical pathways involved in Alzheimer's, including amyloid-beta aggregation and tau phosphorylation.

CRISPR-based strategies could improve the ability of chalcone derivatives to interact with amyloid-beta peptide or modulate the expression of beta-secretase (BACE1), an enzyme involved in amyloid-beta production.

By modifying specific genes involved in tau regulation, CRISPR can help produce chalcones that more effectively prevent or reverse tau-related neurodegeneration.[25]

Anti-inflammatory Applications

CRISPR can be used to enhance their ability to target key signaling pathways involved in inflammation, such as NF-κB and MAPK pathways. This modification can make chalcones more potent in conditions like rheumatoid arthritis, inflammatory bowel disease, and asthma.[26]

A study exploring the CRISPR-modified chalcone derivative 2',4,4'-trihydroxychalcone showed enhanced selectivity for inducing apoptosis in breast cancer cells by modifying its interaction with the p53 pathway.

CRISPR-based modifications of metabolic enzymes in cell lines further demonstrated improved bioavailability and anticancer potency, with lower toxicity to normal cells.

Currently, there are no clinical trials directly using CRISPR-modified chalcone derivatives, but the preclinical successes suggest that such trials could be on the horizon. Future clinical research will likely focus on the pharmacodynamics and pharmacokinetics of CRISPR-modified chalcones. Safety profiles in human subjects, especially regarding the off-target effects of CRISPR editing.[27]

Challenges and Ethical Considerations

One of the primary concerns in CRISPR technology is the possibility of off-target effects, where the CRISPR/Cas9 system may unintentionally edit DNA at sites other than the intended target.

Off-target mutations in genes unrelated to the biosynthetic pathway could compromise the integrity of the engineered plant or microbial system, potentially affecting the production of chalcones or introducing undesired compounds. When targeting human cells for therapeutic purposes (e.g., in cancer treatment), off-target edits could lead to unpredictable outcomes such as cancerous growth or toxicity.[28]

For chalcones, particularly those derived from plants or microbes, researchers must demonstrate:

- Safety of the final product for human consumption.
- Environmental impact of the modified organisms or plants.
- Consistency of chalcone production under different conditions.

CRISPR-CasX and CRISPR-CasY

Newer Cas proteins, such as CasX and CasY, are emerging as even more efficient and precise tools for gene editing. These proteins offer smaller sizes and greater versatility compared to Cas9, which could be beneficial for delivering CRISPR systems to a wider range of organisms, including plants and microbes used for chalcone production. Their smaller size allows for easier delivery via viral vectors, which is a key consideration for therapeutic applications.

CRISPR for Epigenetic Modifications

Some CRISPR-based systems can be used to edit epigenetic marks rather than the genetic sequence itself. These epigenetic edits can be employed to control the expression of chalcone biosynthesis genes without altering the underlying DNA sequence. This offers a more subtle approach to controlling chalcone production and could help fine-tune the production of specific chalcone derivatives with minimal long-term genetic changes.

Multiplexed Editing

Multiplexed CRISPR-Cas systems allow the simultaneous editing of multiple genes in a single step. This could enable the engineering of entire biosynthetic pathways for chalcones, enhancing the ability to create complex derivatives with minimal effort.[29] Multiplexing could be particularly valuable in the synthetic biology context, where multiple genes need to be edited to optimize a biosynthetic pathway.

CONCLUSION

In conclusion, the integration of CRISPR technology into chalcone research represents a significant breakthrough in both biosynthesis and therapeutic applications. By enabling precise and efficient gene editing, CRISPR has opened up new possibilities for enhancing the production of chalcones and their derivatives, which have demonstrated promising pharmacological properties in treating diseases such as cancer, neurodegenerative disorders, and inflammatory conditions.

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