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Sabuwar family ta RNA-guided DNA-targeting systems — daban da CRISPR, kuma ba gene-editing tool ba tukuna

Ta binciken microbial genomes, researchers sun gano TIGR-Tas, previously unknown family na RNA-guided systems da ke cut DNA — da two-part guide kuma ba PAM landing site kamar CRISPR. Sun nuna version d'aya programmable ne a human cells amma low efficiency, kuma structure ta nuna deep evolutionary links zuwa sauran RNA-guided machines. Real expansion ne na RNA-guided biology da possible starting point ga future tools — basic-science discovery da proof of concept, ba mature gene editor ko therapy ba.

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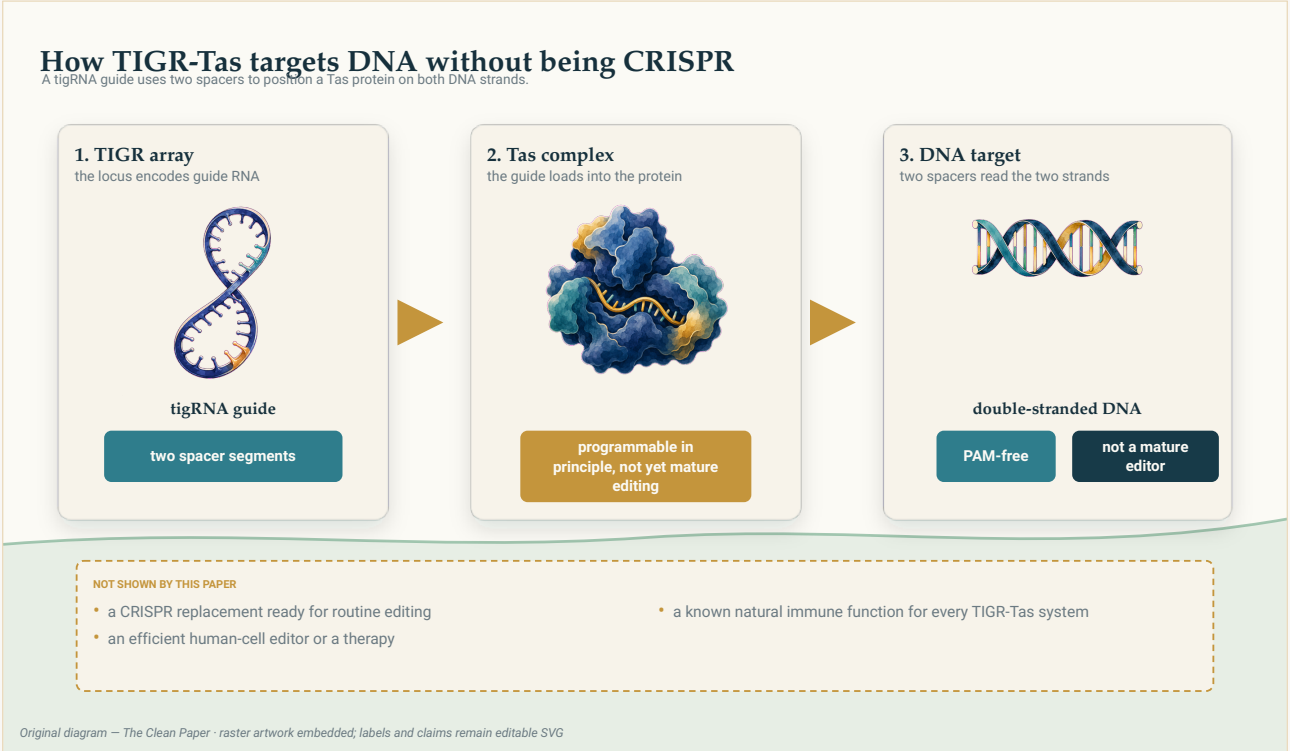
Sabon reshe a bishiyar na’urorin da RNA ke jagoranta

Lokaci-lokaci wata takardar biology tana fitowa da kanun labarin da ita kanta ba ta nema ba. A wannan karon an kira abin “sabon CRISPR.” Aikin da ke bayansa ya fi wannan ban sha’awa — kuma, kamar yadda aka saba, ikirarinsa ya fi ƙanƙanta.

Mu fara da abin da CRISPR ta shahara da shi: **tsarin da RNA ke jagoranta**. Dabarar ita ce protein ba sai an gina shi tun farko domin ya gane target guda ɗaya ba. Maimakon haka yana ɗauke da gajeren RNA — *guide* — sannan ya je inda sequence ɗin guide ya dace. Ka canza guide, ka canza target. Wannan iya shirya target ɗin ne ya sa CRISPR ta zama kayan aiki mai ƙarfi. Amma CRISPR ba ita kaɗai ce irin wannan tsarin a nature ba, kuma tambayar wannan takarda ita ce mai natsuwa: wasu nau’ikan nawa ne suke akwai, kuma me za su iya koya mana?



TIGR-Tas tana amfani da guide mai sassa biyu da ke karanta strands biyu masu kishiyantar juna na DNA. Wannan sabon tsarin architecture ne, ba gene editor da ya shirya don amfani ba.

Don neman ’yan uwa masu nisa, marubutan ba su nemi gene sequences masu kama da juna ba — domin sequences na iya canzawa sosai a tsawon evolution. Sun nemi **siffar proteins**. Sun fara daga ɓangaren Cas9 na CRISPR da ke riƙe guide RNA, sannan suka bincika manyan databases na predicted protein structures domin gano proteins da aka gina da irin wannan siffa. Wannan binciken ya bi wata hanya daga bacterial “jumping gene” da wata machinery da ordinary cells suke amfani da ita wajen yin chemical modification ga RNA, har ya kai ga wani tsarin da ba a taɓa bayyana shi ba.

Abin da marubutan suka yi

Binciken structural ya gano wata family ta proteins da ba a san ta ba, waɗanda aka fi samun genes ɗinsu a bacteriophages — viruses da ke kamuwa da bacteria — da viruses na archaea, da kuma ƙananan parasitic bacteria. Kowane protein yana kusa da wani sashe na DNA mai maimaitawa da tsari na musamman: dogon array da marubutan suka kira **TIGR array** (*Tandem Interspaced Guide RNA*). Sun kira proteins ɗin **Tas** (*TIGR-associated*). Wasu Tas suna da ɓangaren riƙe RNA kawai; wasu kuma suna da wani kayan yanke DNA, ɗaya daga nau'ikan molecular scissors biyu da ake kira RuvC ko HNH.

Bayan gano family ɗin a databases, sai suka kai tsarin dakin gwaje-gwaje. Sun sa systems ɗin su bayyana a *E. coli*, suka sequencing ƙananan RNA da suka samar, suka gano ƙa'idar da RNAs ɗin ke amfani da ita wajen gano DNA target, suka gwada ko versions masu nuclease suna yanke DNA da gaske, suka yi ƙoƙarin shirya ɗaya domin editing a human cells, sannan a ƙarshe suka daskare active complex suka ɗauki hoton structure ɗinsa a kusan atomic resolution.

Abin da suka gano

Guide RNA ɗin yana da sassan targeting biyu. Ana sarrafa TIGR array zuwa ƙananan RNAs masu kusan haruffa 36, kowannensu yana ɗauke da **sassa biyu daban** da ke gano target. Ɗaya yana karanta strand ɗaya na DNA, ɗayan kuma strand ɗin kishiyarsa. Sassan biyu suna aiki tare domin kulle target. Wannan ya bambanta da CRISPR, inda guide yawanci yake da continuous stretch guda da ya dace da strand ɗaya.

Kuma ba ya buƙatar "landing pad." Nucleases da yawa na CRISPR suna iya yanke DNA ne kawai idan akwai gajeren specific motif, **PAM**, kusa da target. Wannan yana takaita wuraren da za a iya nufi. TIGR systems ba su nuna irin wannan requirement ba: target sequence kaɗai ya isa. A principle, tsarin da ba ya buƙatar PAM zai iya kaiwa wurare fiye da na'urar da ke buƙatarsa.

Versions masu nuclease sun yanke DNA daidai. Da guide RNA ɗinsu, Tas proteins masu RuvC ko HNH sun yi sequence-specific breaks masu tsabta a DNA. Ba tare da guide ba, ba su yanke target ba.

An iya shirya version guda domin editing human cells — amma da ƙaramin inganci. Da aka saka wani Tas protein cikin human cells a dish aka nufi genes shida daban-daban, ya yi edits. Wannan ya nuna cewa tsarin yana iya programmability a cells ɗinmu ma. Amma efficiency ya yi ƙasa: a mafi kyau, cells kaɗan cikin ɗari ne aka gyara. Optimized CRISPR tools na yau suna iya edit babban kaso na cells. Don haka wannan hujja ce cewa **yana iya aiki**, ba kayan da yake aiki **da kyau** ba tukuna.

Structure ɗin ya bayyana mechanism — kuma ya ba da alamar asalinsa. Complex ɗin da aka ɗauki hotonsa proteins biyu ne masu symmetry kamar madubi suna riƙe guide RNA mai siffar figure-eight, yayin da target DNA ya lanƙwashe cikin sharp turn. Abin mamaki, wannan architecture yana kama sosai da **box C/D snoRNP**, machinery da cells masu alaƙa da namu suke amfani da ita wajen jagorantar chemical edits ga RNA maimakon yanke DNA.

Aikin sa na halitta har yanzu ba a sani ba. Da marubutan suka bayyana wani system a *E. coli*, bai kare cell daga viruses ko plasmids masu mamaye ta ba — aikin da CRISPR ta fi shahara da shi. Maimakon haka, a hankali ya rage targeted plasmid a tsawon generations da yawa. Wannan yana iya nuna cewa aikin sa na gaske yana cikin

gasa mai jinkiri tsakanin mobile DNA elements, ba front-line immune defence ba. Amma wannan gwaji ne a wani artificial host, don haka amsar da ta fi gaskiya ita ce: **ba mu san abin da TIGR-Tas take yi a daji ba tukuna.**

Abin da wannan yake iya nufi

Akwai ra'ayoyi biyu, amma matakin amincewa da su ya bambanta.

Na farko yana da ƙarfi: duniyar RNA-guided systems ta fi CRISPR da 'yan uwanta da aka gano kwanan nan faɗi da bambance-bambance. TIGR-Tas reshe ne dabam da gaske, tare da guide mai sassa biyu da kuma hanyar gano DNA ba tare da PAM ba. Wannan ƙarin abu ne na gaske a taswirar biology.

Na biyu ya fi zurfi amma ya fi speculative: saboda TIGR machinery an gina ta kamar snoRNP da ke gyara RNA a cells irin namu, kuma tana da alaƙar structure da wani jumping gene, wataƙila tana nuna **mahada ta evolution** tsakanin RNA-guided systems da ke gyara RNA da waɗanda ke targeting DNA. Wannan na iya zama wani ɓangare da ya ɓace a tarihin yadda programmable RNA guides suka taso a sassa daban na rayuwa.

Abin da wannan binciken bai tabbatar ba

- **Ba gene-editing tool da ya shirya ba ne.** An nuna editing a human cells, amma efficiency ɗin kaɗan ne — a mafi kyau 'yan kashi cikin ɗari. Wannan proof of programmability ne, ba mature editor ba, kuma yana da nisa da amfani na asibiti.
- **Ba "CRISPR 2.0" ba ne.** Idan an kwatanta su a matsayin tools na yau, CRISPR-Cas9 ya fi shi editing sosai. TIGR-Tas sabon architecture ne a proof-of-concept stage, ba ingantacciyar sigar wani existing product ba.
- **Aikin sa na halitta ba a sani ba.** Bai yi anti-virus immune defence a gwajin da aka yi ba; saboda haka ba a tabbatar da cewa "sabon bacterial immune system" ba ne.
- **Har yanzu akwai muhimman tambayoyi game da mechanism**, ciki har da yadda guide RNA ake yanke shi zuwa final length da abin da systems ɗin suke targeting a nature. Yawancinsu suna cikin microbes da ba mu iya culture da sauƙi ba.
- **Babu therapy a nan.** Wannan discovery da characterisation ne a microbes da cell culture — babu cuta, babu magani, babu mara lafiya.

Yaya ƙarfin shaidar yake?

Gano family ɗin kansa yana kan ƙaƙƙarfan tushe kuma shaidarsa ta zo daga hanyoyi da yawa: large-scale structural mining, laboratory confirmation na yadda RNA ake samarwa da yadda yake gano da yanke DNA, near-atomic structure na active complex, da human-cell test. Ikirarin cewa "wannan sabon distinct family ne na RNA-guided DNA-targeting systems" yana samun goyon baya daga bangarori da dama tare.

Abin da har yanzu yake farkon mataki shi ne **amfanin sa a matsayin tool**. Editing ya yi aiki, amma da ƙaramin efficiency, kuma duk optimization da ya mayar da CRISPR daga abin mamaki zuwa kayan aiki yana gaban TIGR.

Abin da ya fi dogara da inference kuwa shi ne labarin natural role da evolution: natural role hasashe ne mai ma'ana daga gwaji na artificial setting, kuma proposed evolutionary link, ko da yake tana da kyau, hujja ce daga shared structure, ba tabbataccen tarihin evolution ba. Takardar ta ware wadannan matakan da kyau.

Me ya sa wannan yake da muhimmanci

Fadada catalogue na RNA-guided systems a baya ya ba da tools masu amfani daga baya. Cas9, Cas12, Cas13, kananan IscB/OMEGA proteins da eukaryotic Fanzors dukkansu sun fara ne a matsayin sabon biology da aka gano, ba finished products ba. Tsarin da ke da guide mai sassa biyu kuma ba ya bukatar PAM wani sabon starting point ne, kuma PAM-free targeting irin flexibility ce da masu gina tools suke so.

Amma watakila sakamakon da ya fi shiru ya fi muhimmanci fiye da yiwuwar tool. Ta hada DNA-cutting system da RNA-editing snoRNP machinery da kuma jumping gene, aikin yana zana wata yiwuwar hanyar hadi tsakanin RNA-guided systems daban-daban a bishiyar rayuwa. Irin wannan finding na iya sake tsara yadda fannin yake fahimtar asalin tools dinsa — wanda a dogon lokaci zai iya zama mafi daraja fiye da wani kanun labari game da "molecular scissors."

Takaitaccen bayani

Ta hanyar neman **siffar proteins** maimakon sequences, masu bincike sun gano **TIGR-Tas**, wata family da ba a sani ba ta RNA-guided DNA-targeting systems, wadda aka fi samu a viruses na bacteria da parasitic bacteria. Guide RNA dinta ba na yau da kullum ba ne: kusan haruffa 36 ne kuma yana dauke da sassan targeting biyu da ke karanta strands biyu masu kishiyantar juna na DNA. Ba kamar CRISPR da yawa ba, tsarin ba ya bukatar PAM kusa da target. Members masu nuclease suna yanke DNA daidai; an iya shirya daya domin edit human cells, amma efficiency ya kasance kadan cikin dari; kuma near-atomic structure ya nuna complex da ya yi kama da snoRNP machinery da ke gyara RNA a cells irin namu. Wannan yana ba da yiwuwar deep evolutionary link tsakanin RNA-guided RNA-modifying da DNA-targeting systems. Wannan fadada ne na gaske a RNA-guided biology kuma watakila sabon chassis ga tools na gaba — **basic-science discovery da proof of concept**, ba mature gene editor ba, ba "CRISPR 2.0" ba, kuma ba therapy ba. Natural role dinsa har yanzu ba a sani ba.

Bincike ba tare da karin gishiri ba

Abin da takardar ta nuna: Sabon distinct family na RNA-guided DNA-targeting systems, TIGR-Tas, a prokaryotes da viruses dinsu, wanda aka gano ta structural mining; guide RNA mai sassa biyu, kusan 36 nt, wanda ke targeting strands biyu na DNA ba tare da PAM ba; precise RNA-guided DNA cleavage daga members masu nuclease; programmable editing a human cells da karamin efficiency; near-atomic cryo-EM structure; da structural/evolutionary links zuwa box C/D snoRNPs da IS110 transposons.

Abin da yake yiwuwa amma ba a tabbatar ba: Natural biological role na systems din — gwaji guda na artificial

setting ya nuna yiwuwar gasa tsakanin mobile elements maimakon defence — da proposed evolutionary bridge tsakanin RNA-modifying da DNA-targeting RNA-guided systems.

Abin da bai nuna ba: Mature ko high-efficiency gene-editing tool; superiority ga CRISPR a matsayin tool; confirmed natural function; cikakken mechanism na maturation na guide RNA; ko therapeutic application.

Manyan iyakoki: Human-cell editing efficiency ya yi ƙasa kuma proof of concept ne kawai; yawancin systems suna cikin metagenomes masu wahalar nazari, don haka natural targets ba a sani sosai ba; natural-role da evolutionary-origin claims suna dogara da inference; characterisation ta kasance a microbes da cell culture, ba disease context ba.

Yawan amincewar da ya dace ga mai karatu na gama gari: Babba cewa wannan distinct sabon family ne na RNA-guided DNA-targeting systems da novel two-part, PAM-free mechanism. Babba kuma cewa **ba** gene-editing tool da ya shirya ba ne, ba “CRISPR 2.0” ba, kuma ba therapy ba. Ƙasa game da natural role da yadda zai yi nisa a matsayin tool. Matsayin da ya dace: a yi murna da sabon biology da yiwuwar evolutionary missing link, amma a yi haƙuri da applications — har yanzu suna farkon farawa.

Majiyoyi

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