



COI Disclosure Information

Lead Presenter/Responsible Researcher:

Toshikazu Ushijima

I have the following financial relationships to disclose.

- ✓ **Patents with and research fund from:**
SYSMEX Corporation, Miraca holding Corporation

胃粘膜の発がんリスク とDNAメチル化異常の蓄積

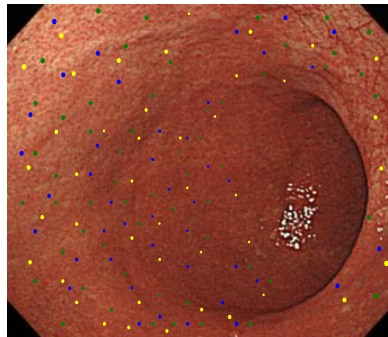
H. pylori (-)



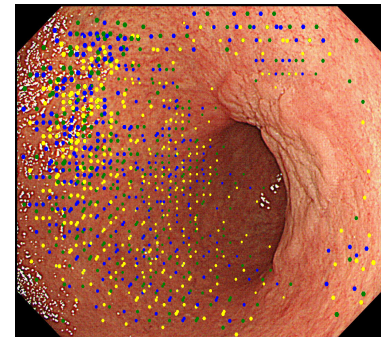
0% /year

(primary gastric cancer)

H. pylori infection, present or past (+)



0.1-1.3% /year



2.5% /year

(metachronous gastric cancer)

Incidence of a next cancer

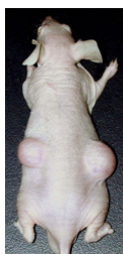
[Ushijima et al., J Gastroenterol, 41:401, 2006; Nat Rev Cancer, 6:172, 2006; Gastroenterol, 131:1647, 2006]

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2. DNAメチル化異常誘発の分子機構
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研究の始まりは「正常組織に異常がある」

LOX suppresses gastric cancer growth

Vector



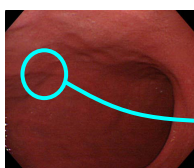
LOX



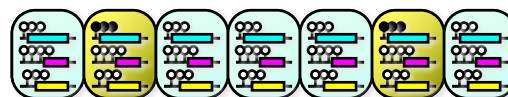
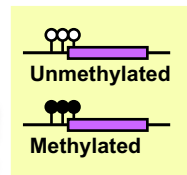
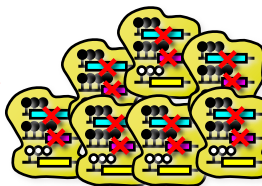
Gastric cancer patient



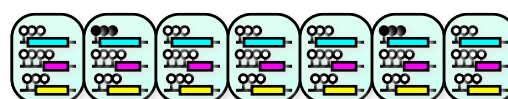
Healthy individual



LOX



Field Defect

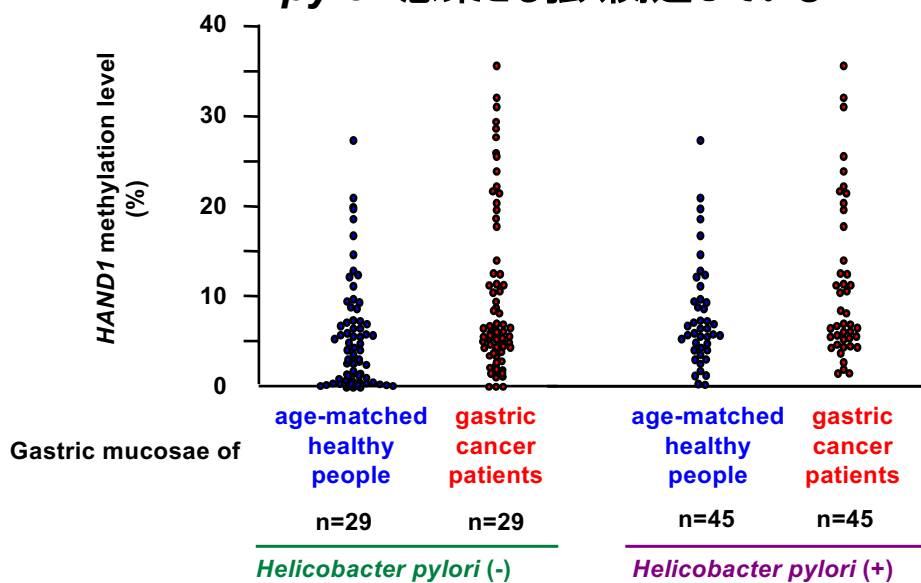


Field Present

[Kaneda et al., Cancer Res 64; 6410-6415, 2004]

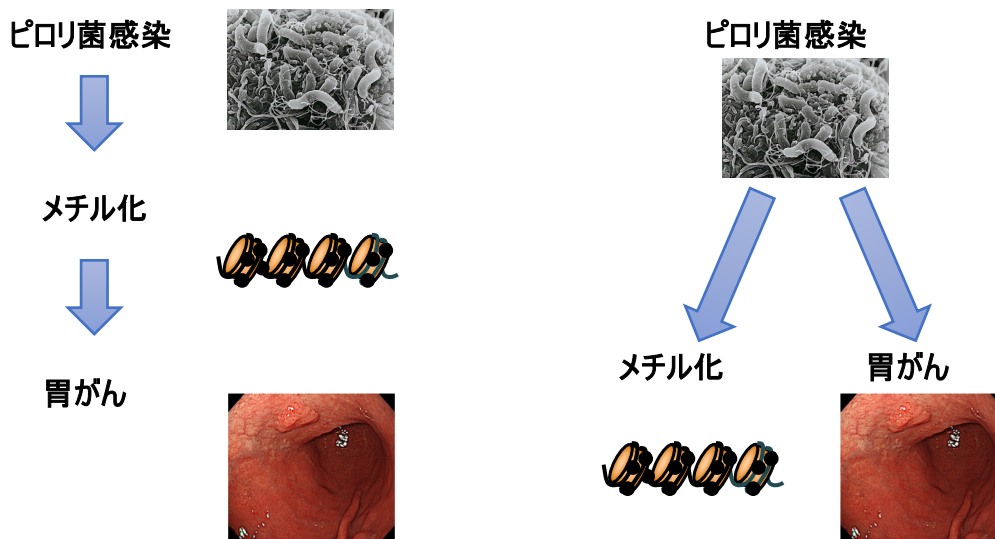
[Kaneda et al., Cancer Res., 62: 6645, 2002]

正常胃粘膜のDNAメチル化異常の程度は発がんリスクと関連していて *H. pylori*感染とも強く関連している



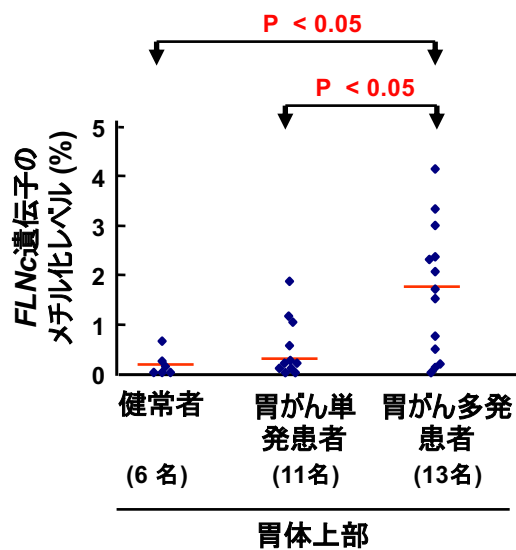
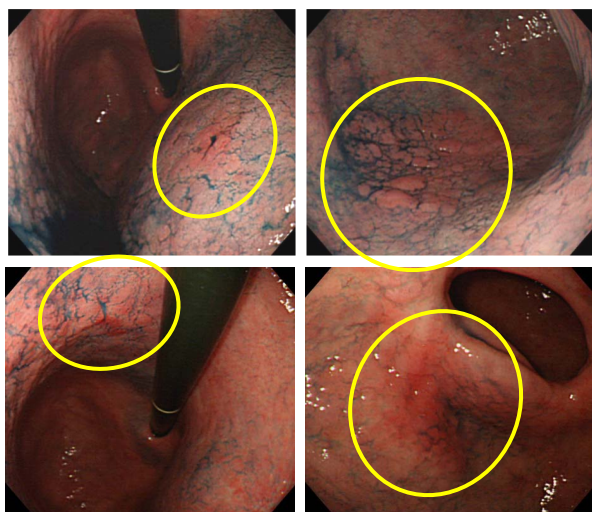
[Maekita et al., Clin Cancer Res, 12:989, 2006]

DNAメチル化がたまることが、本当にがんの原因だろうか？



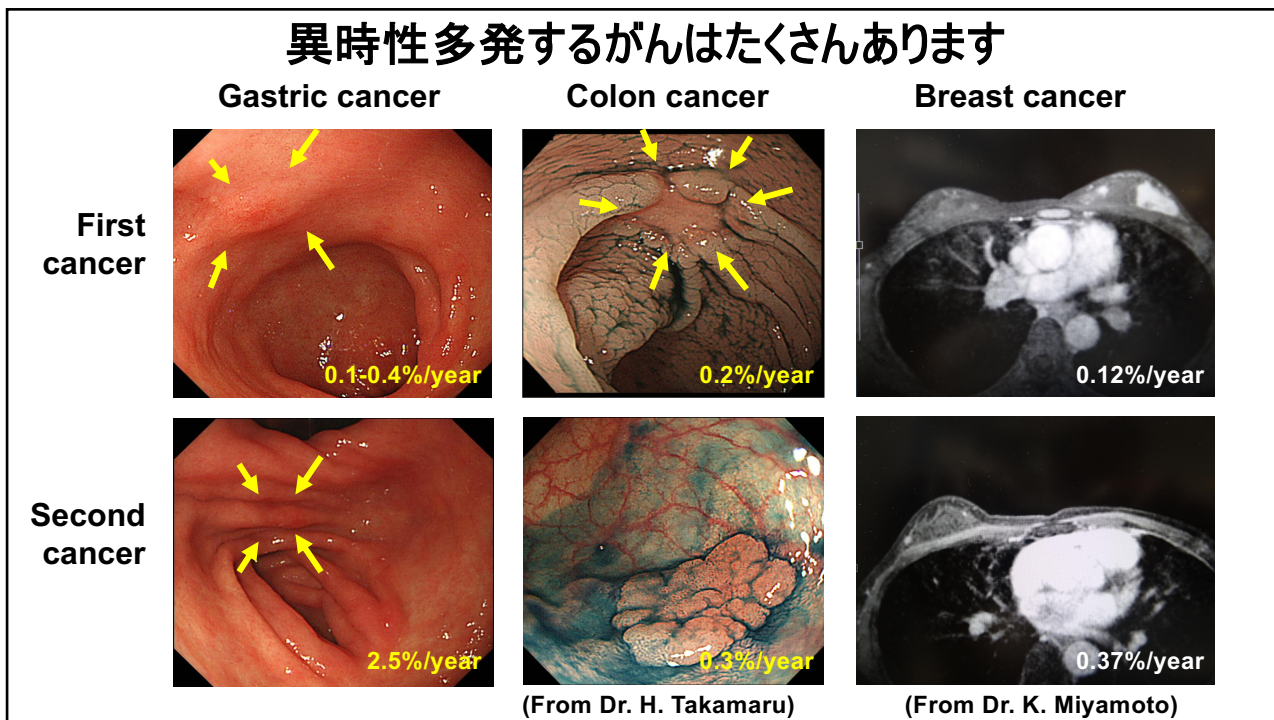
DNAメチル化の蓄積は多発胃がん患者の方が高度で、やはり、DNAメチル化の蓄積が胃がんの原因らしい

一生の間に7個胃がんを発症した人

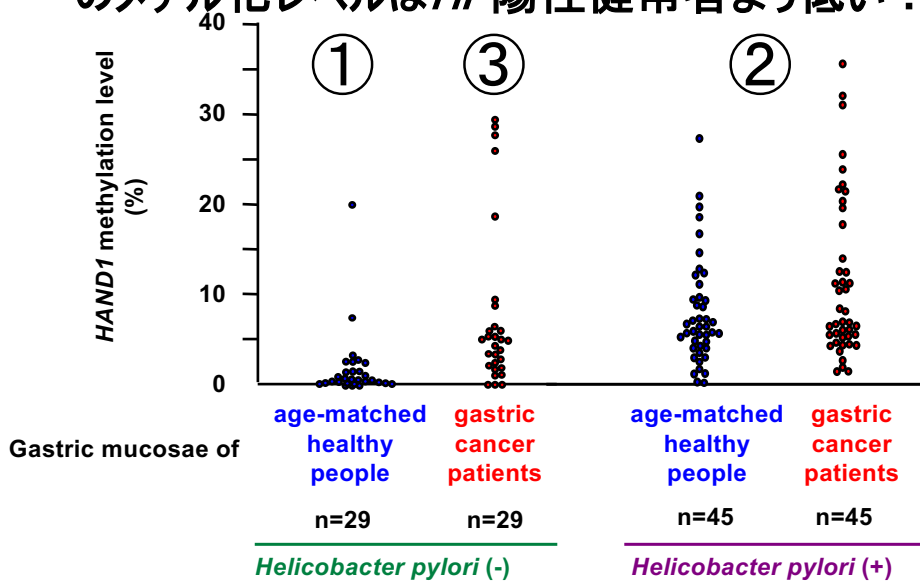


[Nakajima et al., CEBP, 15:2317, 2006]

異時性多発するがんはたくさんあります

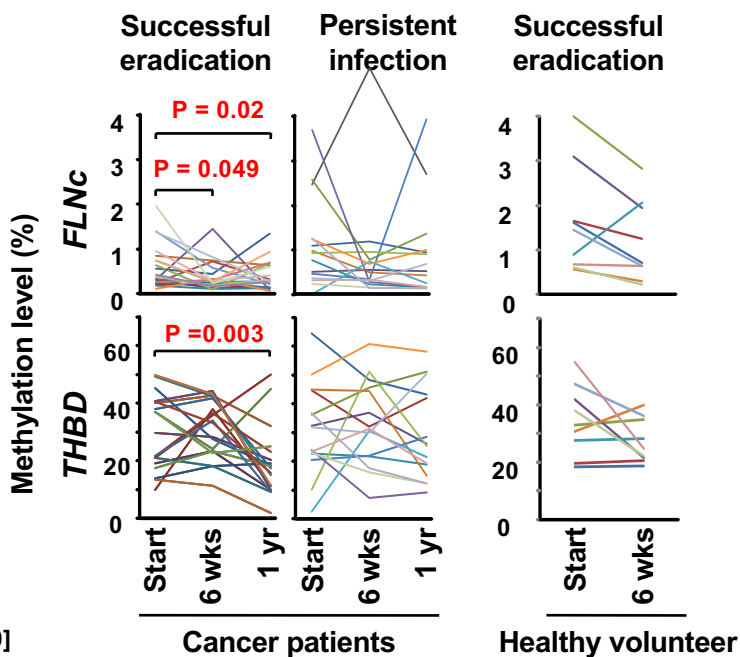
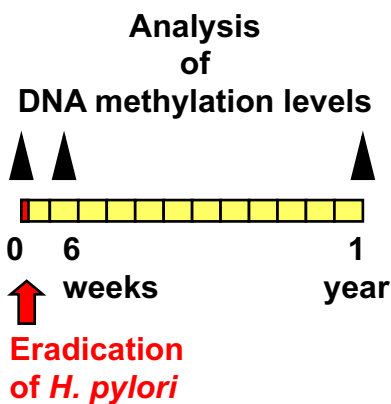


もう一つの疑問:なぜ「HP陰性」胃がん患者(=HP過去感染者)のメチル化レベルはHP陽性健常者より低い?



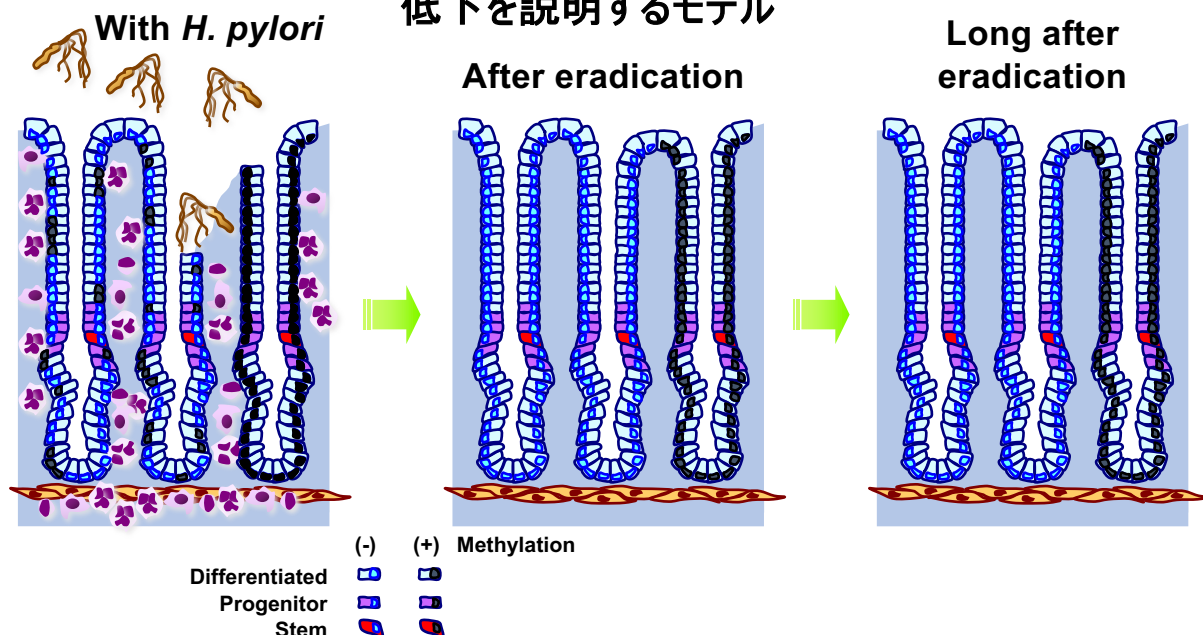
[Maekita et al., Clin Cancer Res, 12:989, 2006]

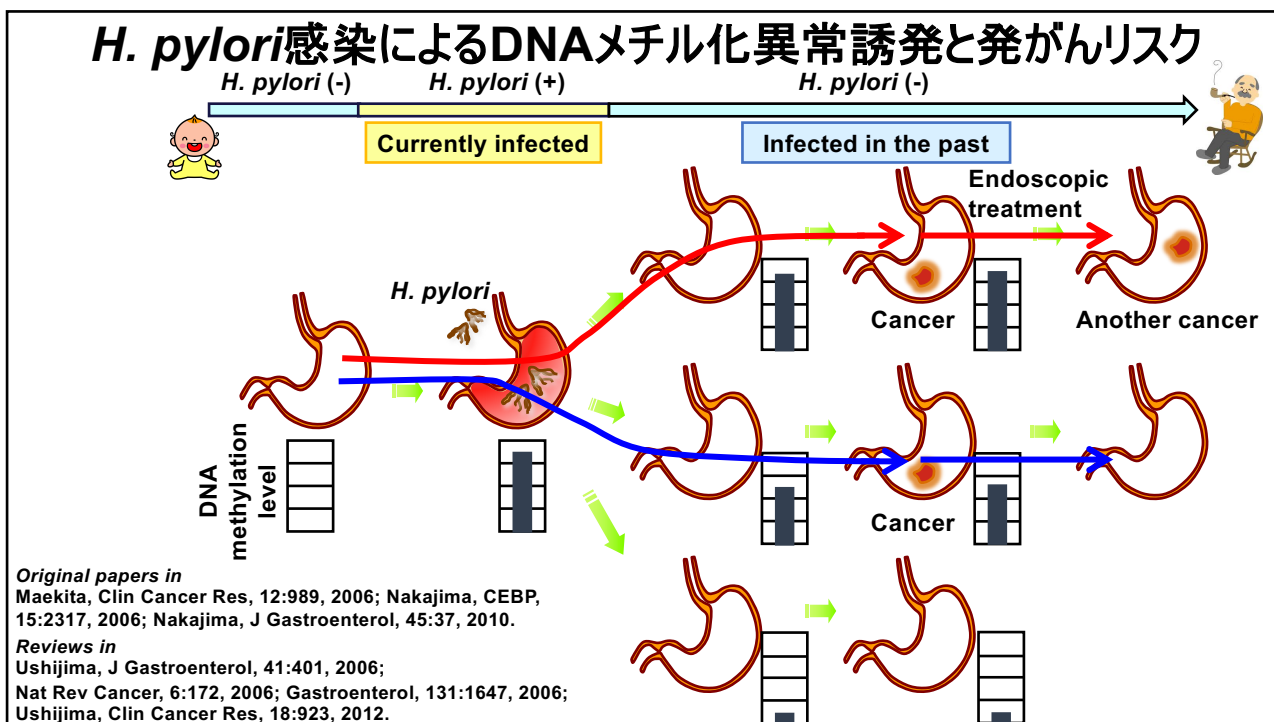
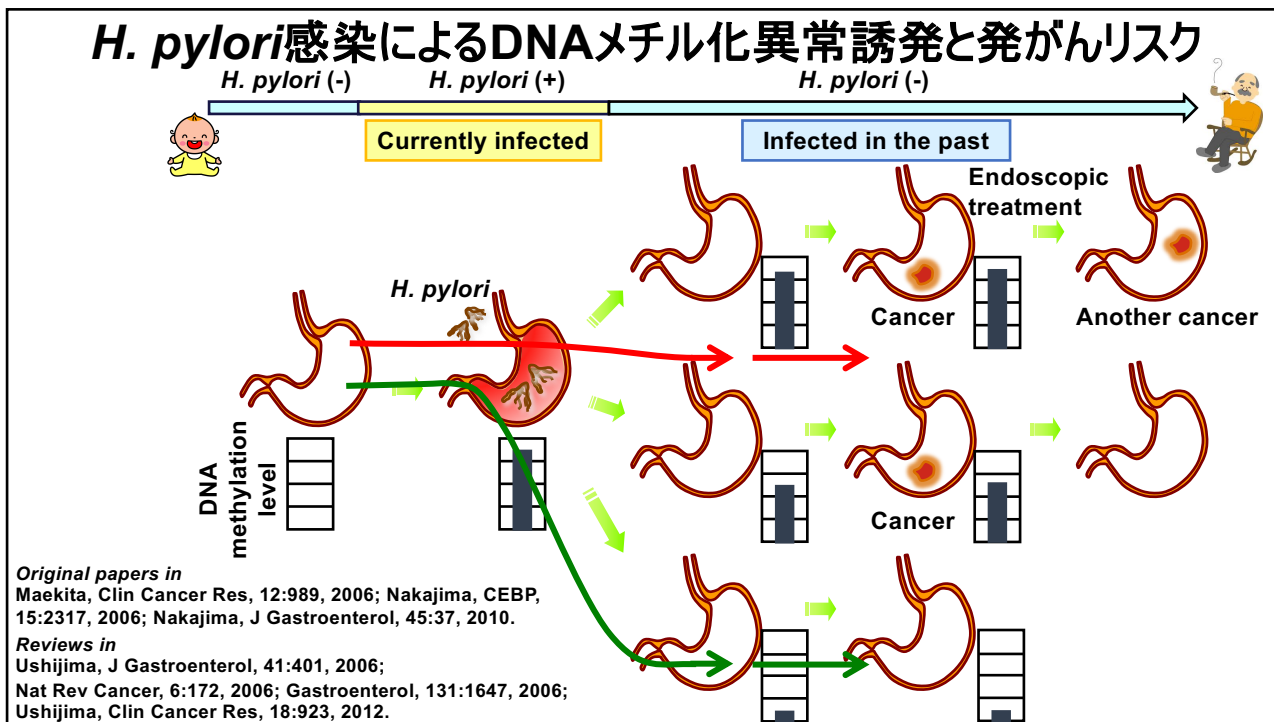
H. pylori除菌によるDNAメチル化レベルの低下



[Nakajima et al, J Gastroenterol, 45:37, 2010]

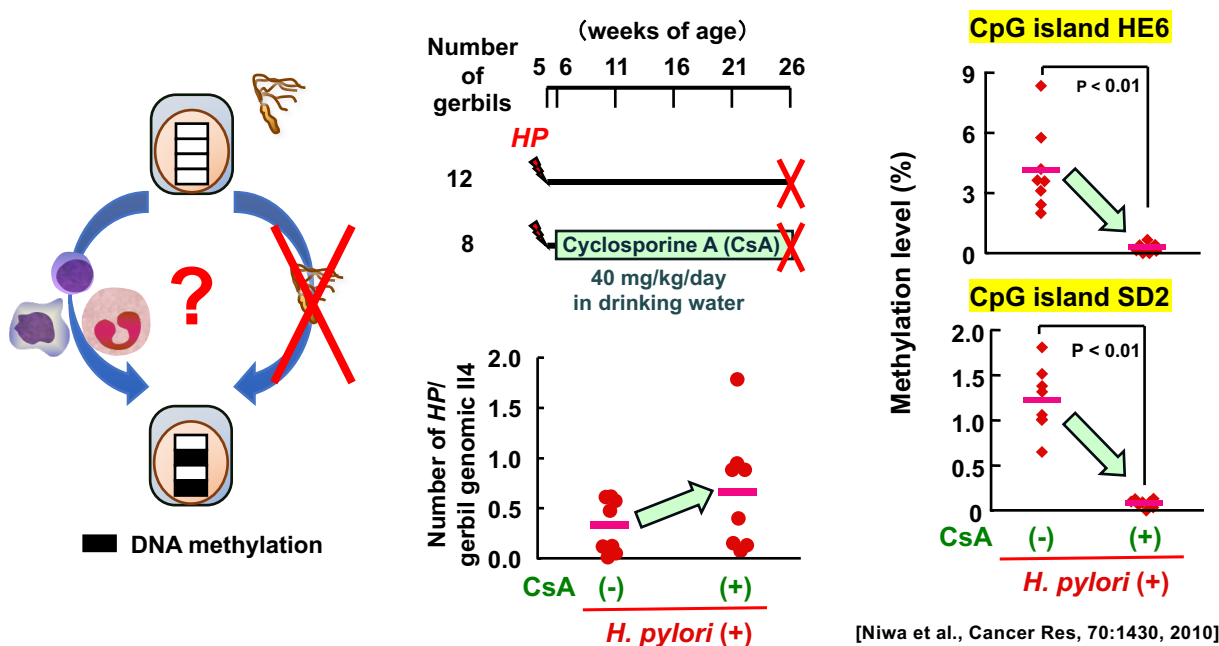
細胞の分化度に応じたメチル化誘発感受性の違いにより、メチル化低下を説明するモデル



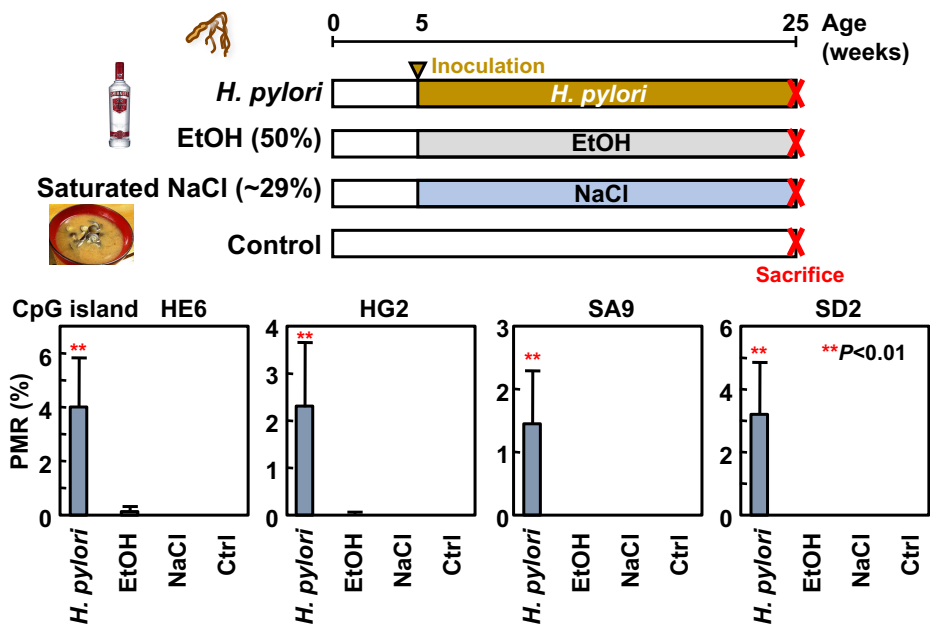


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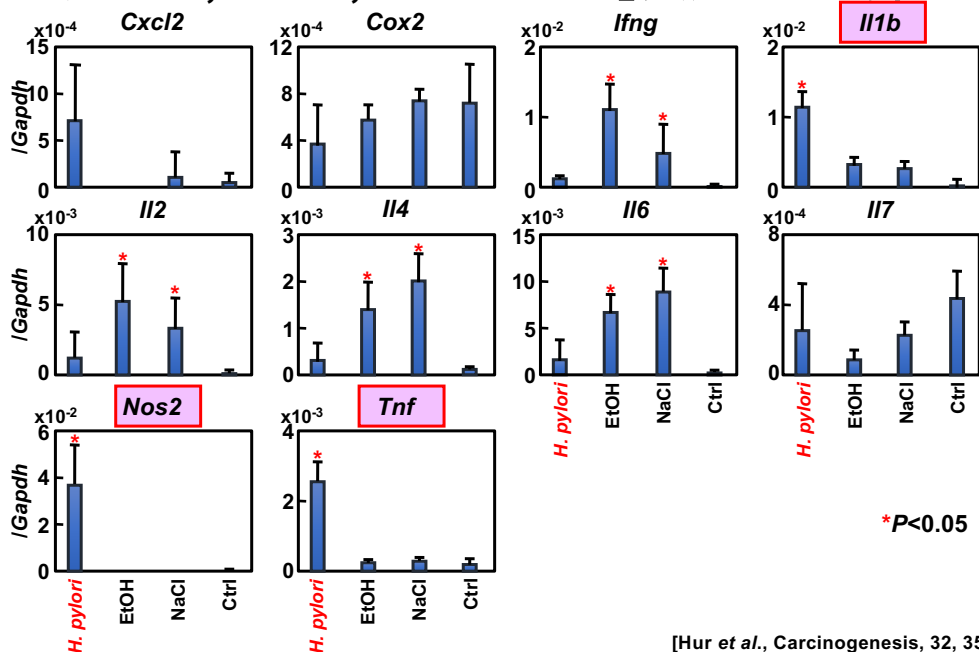
~~ピロリ菌が悪いのか？~~ 炎症が悪いのか？



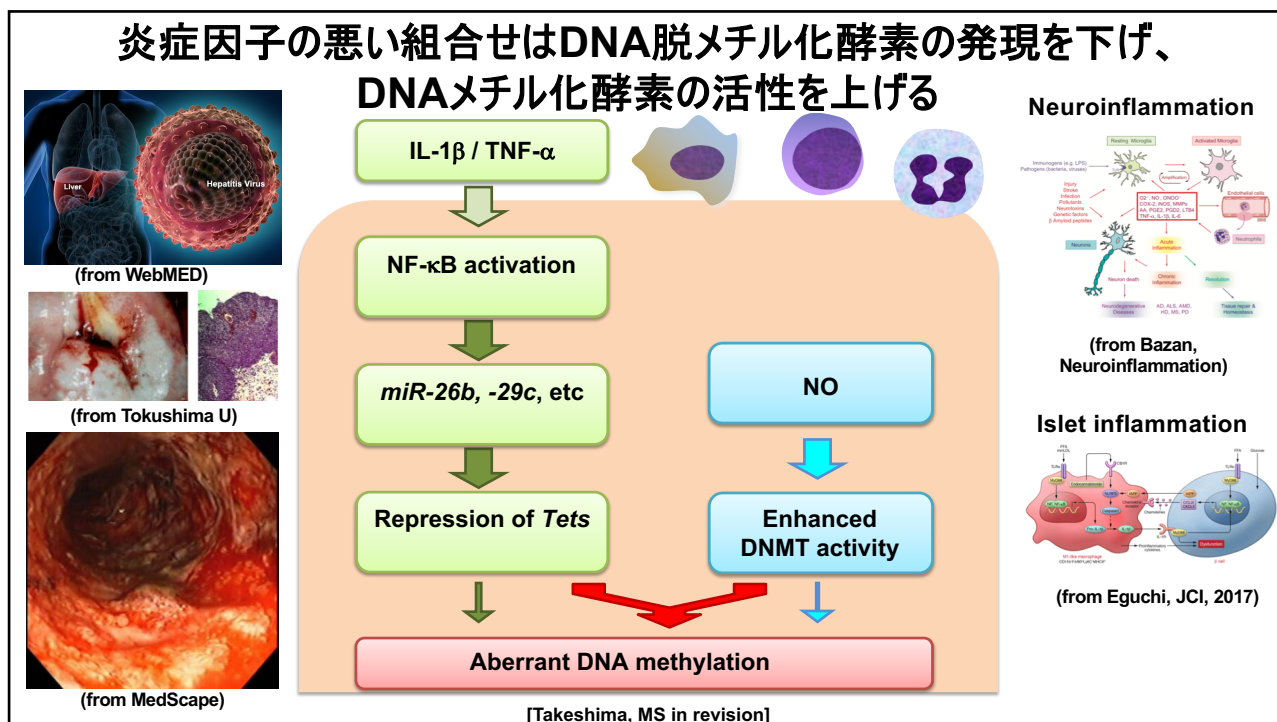
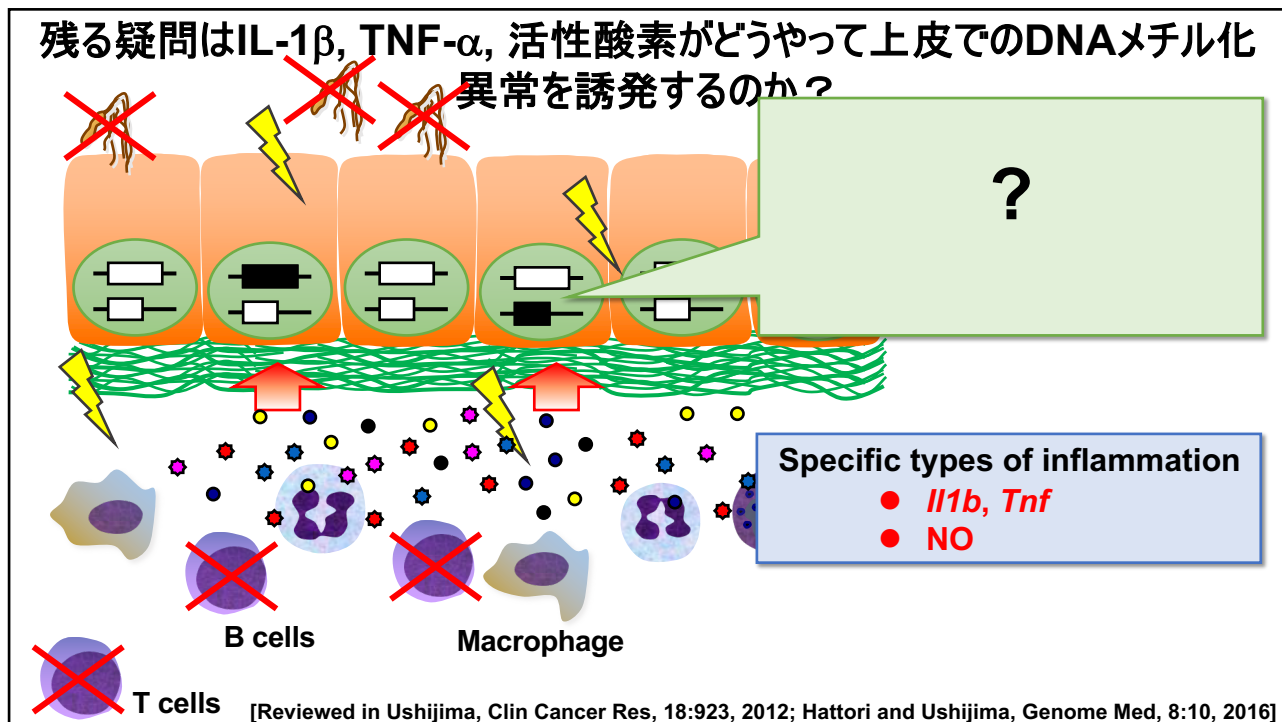
では、炎症なら何でもDNAメチル化異常を誘発するのだろうか？



どうも*Il1b*, *Nos2*, *Tnf*が「悪い」炎症では上昇してくる



[Hur et al., Carcinogenesis, 32, 35-41, 2011]

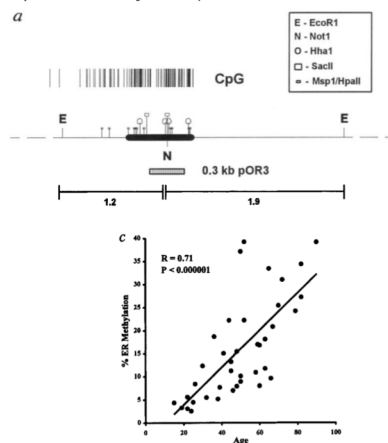


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DNAメチル化異常の原因は加齢、炎症による加速、とされる

Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon

Jean-Pierre J. Issa, Yvonne L. Ottaviano, Paul Celano, Stanley R. Hamilton¹, Nancy E. Davidson & Stephen B. Baylin²

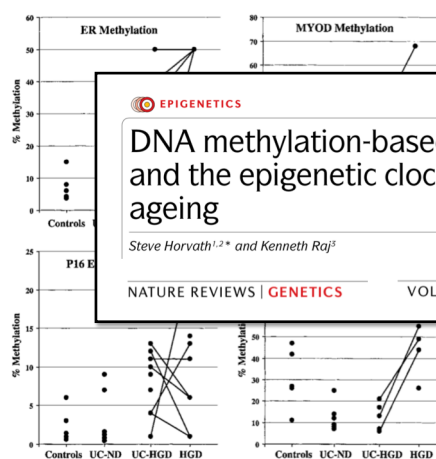


[CANCER RESEARCH 61, 3573-3577, May 1, 2001]

Advances in Brief

Accelerated Age-related CpG Island Methylation in Ulcerative Colitis¹

Jean-Pierre J. Issa,² Nita Ahuja, Minoru Toyota, Mary P. Bronner, and Teresa A. Brentnall



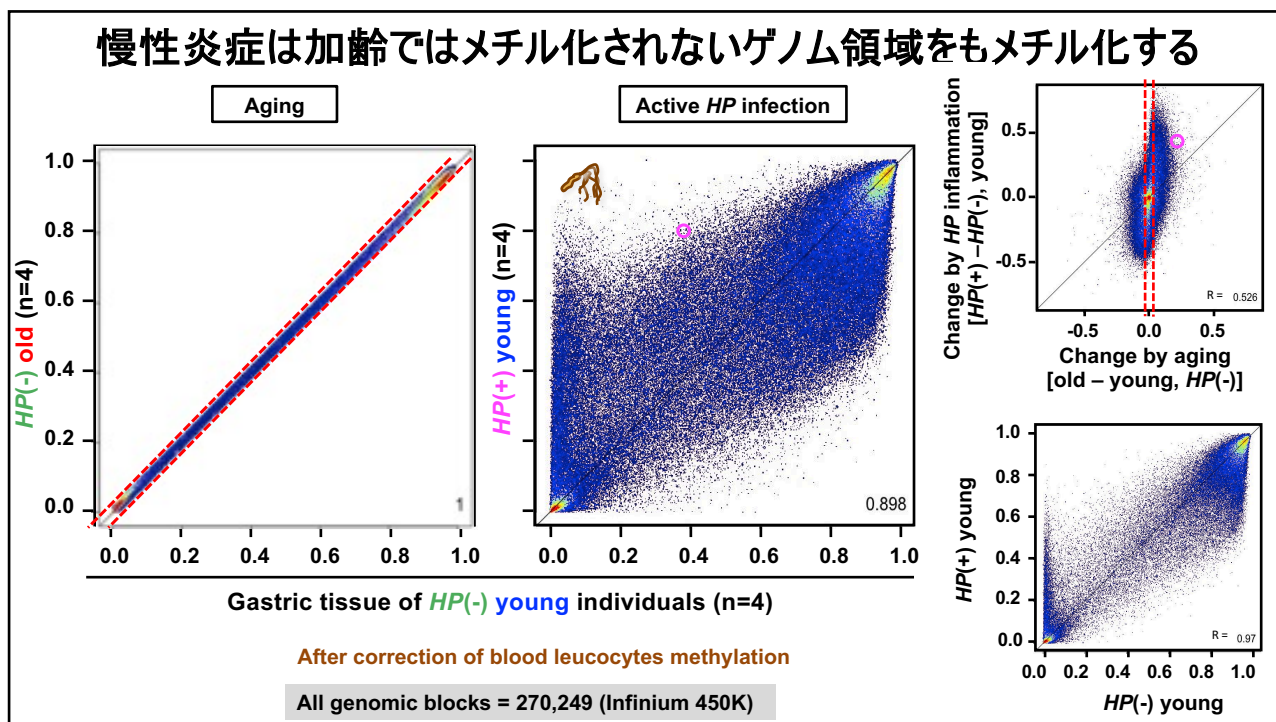
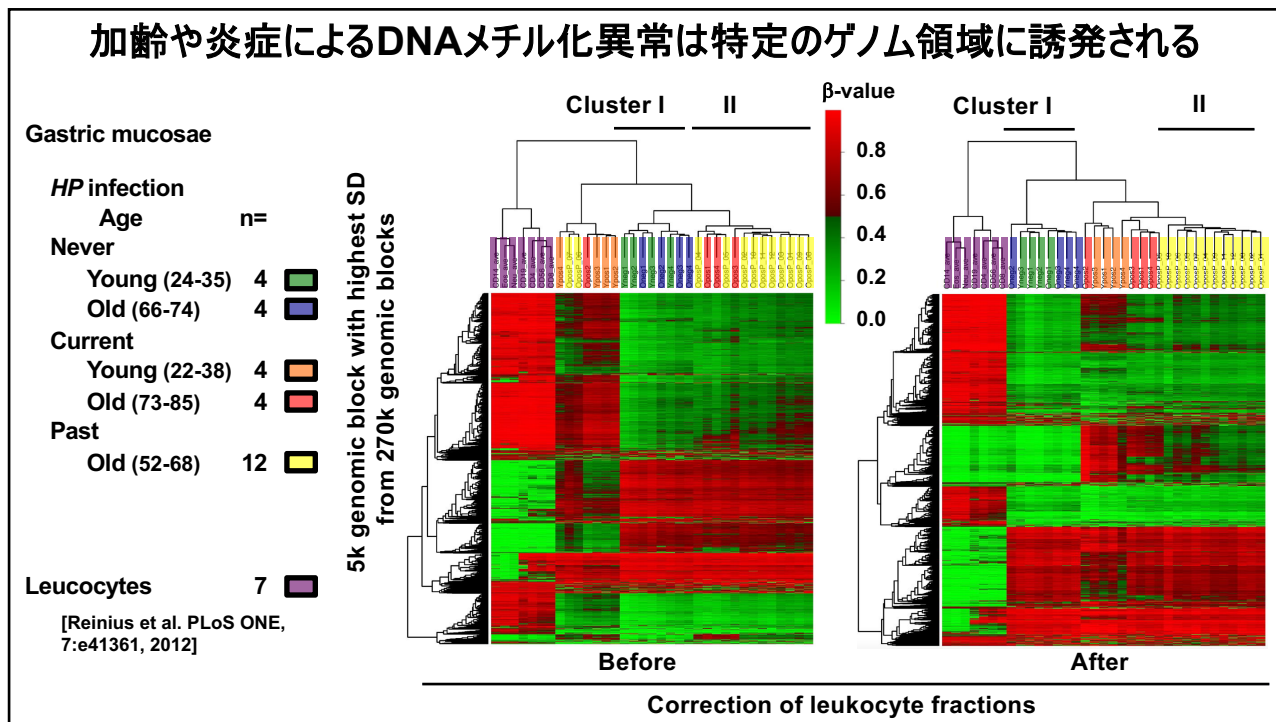
EPIGENETICS

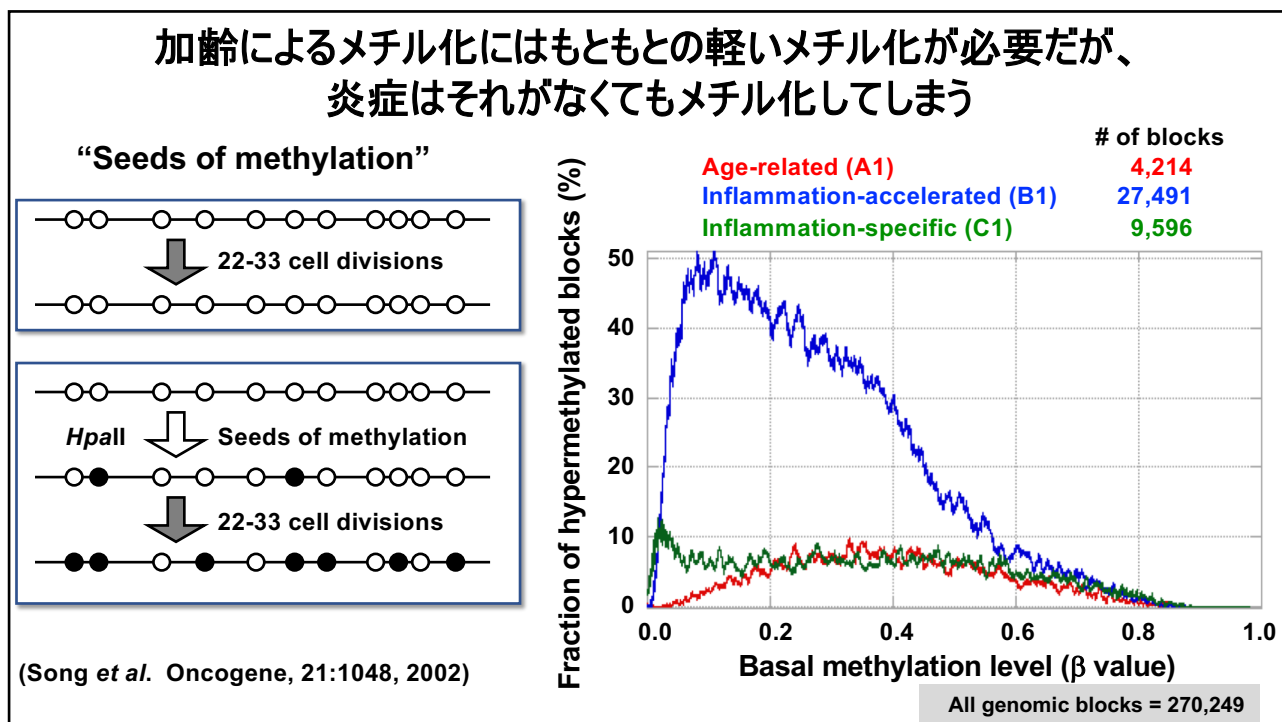
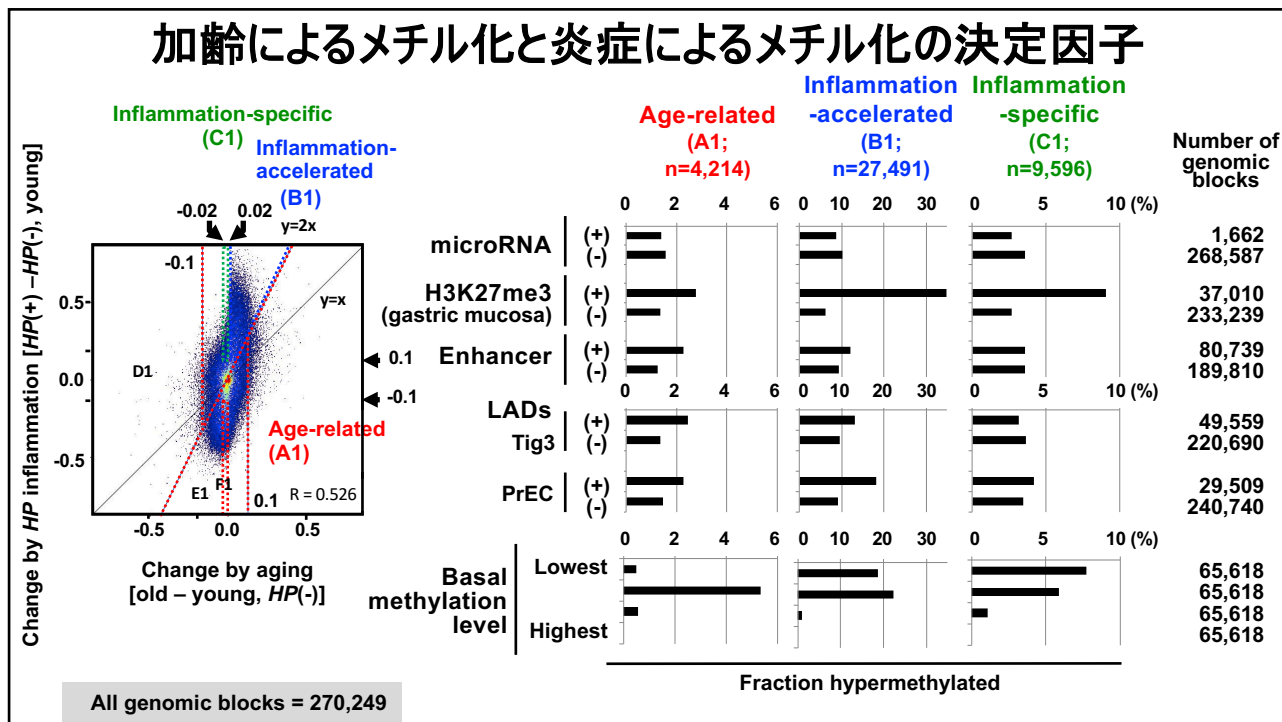
DNA methylation-based biomarkers and the epigenetic clock theory of ageing

Steve Horvath^{1,2*} and Kenneth Raj³

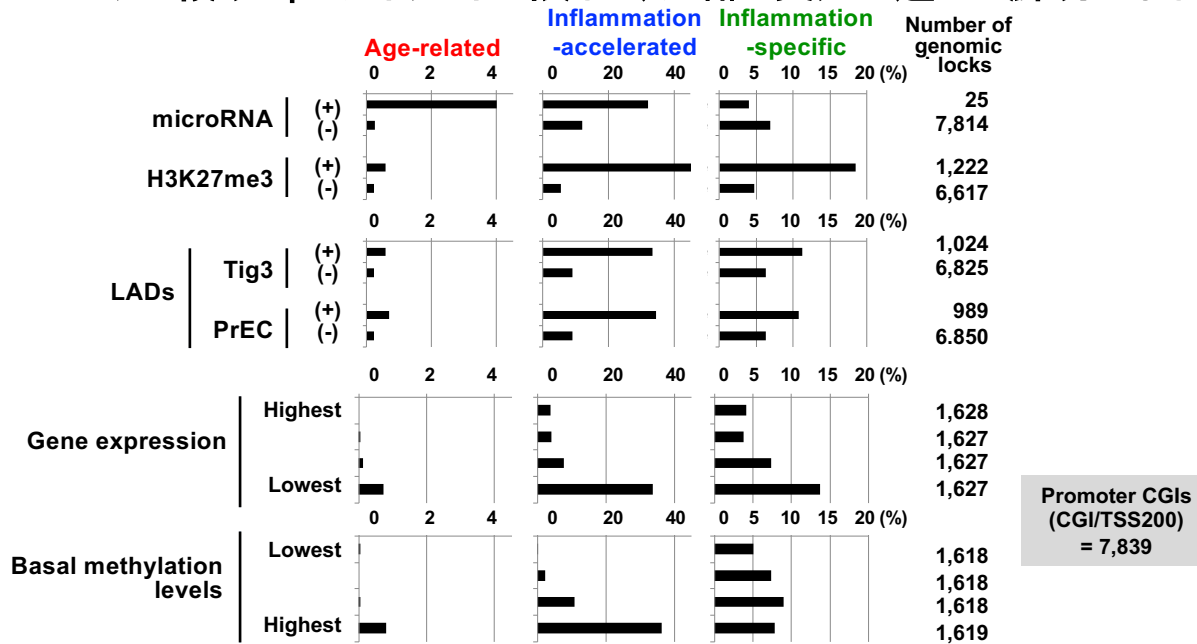
NATURE REVIEWS | GENETICS

VOLUME 19 | JUNE 2018 | 371

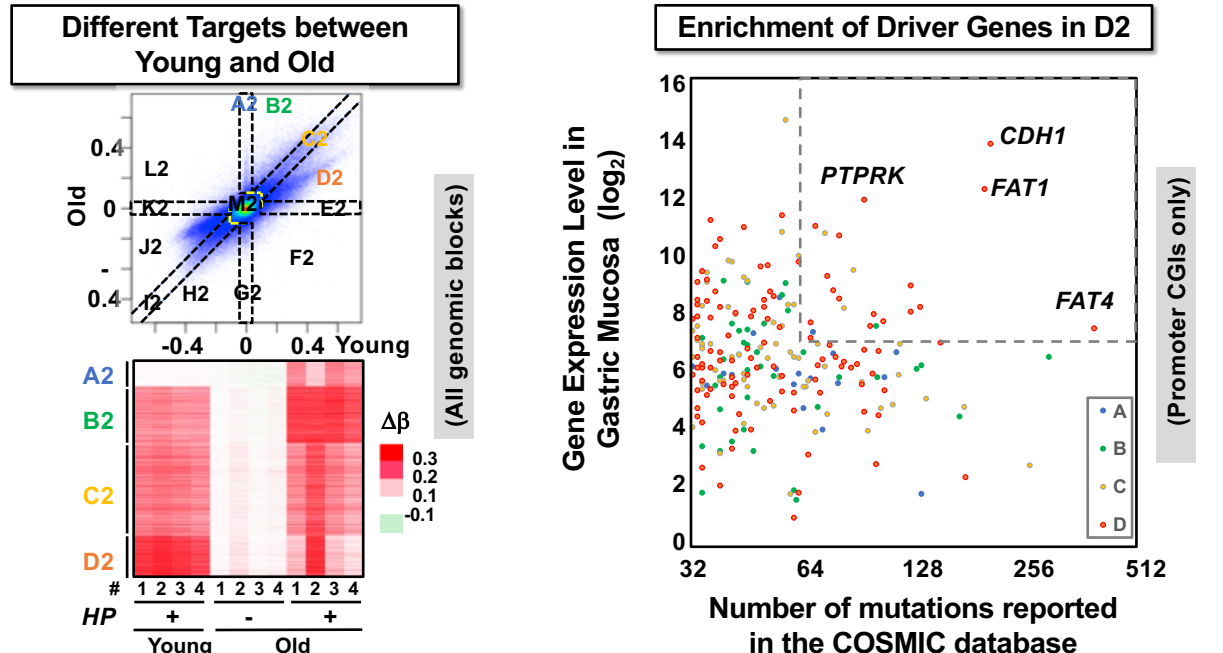



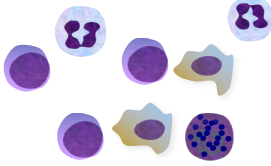


プロモーター領域CpGアイランドに限ると、加齢と炎症の違いが鮮明になる



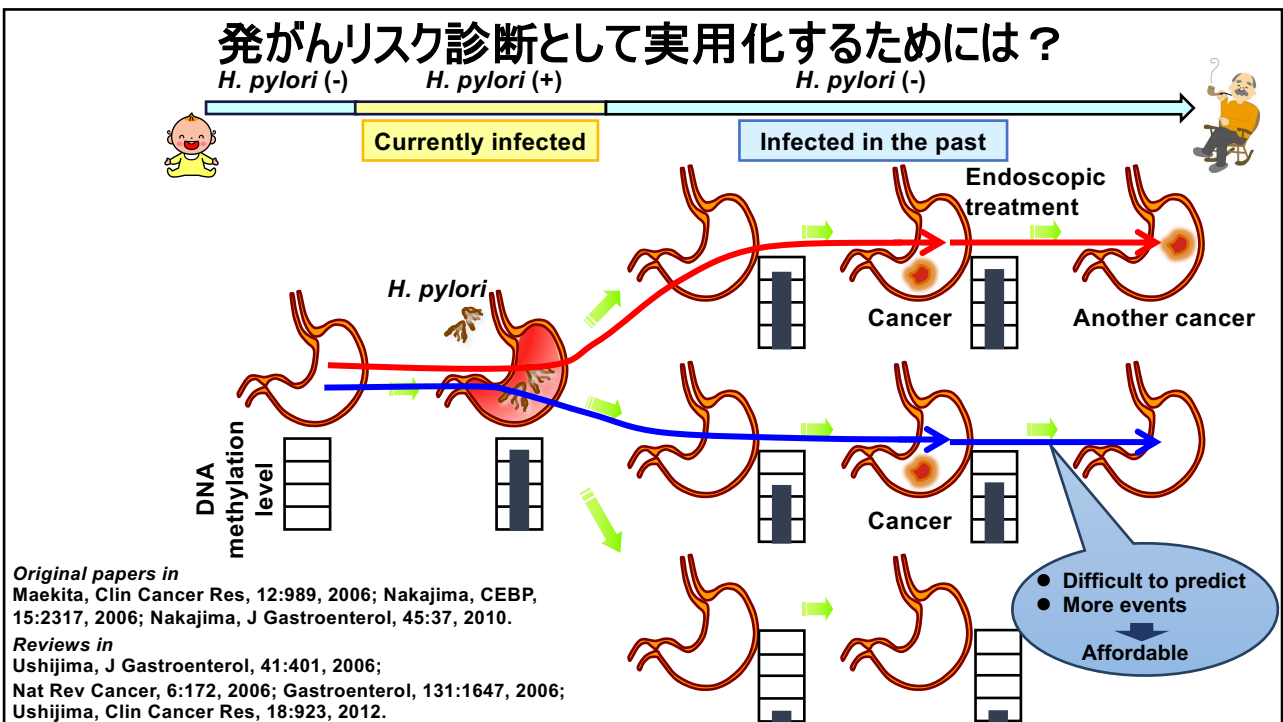
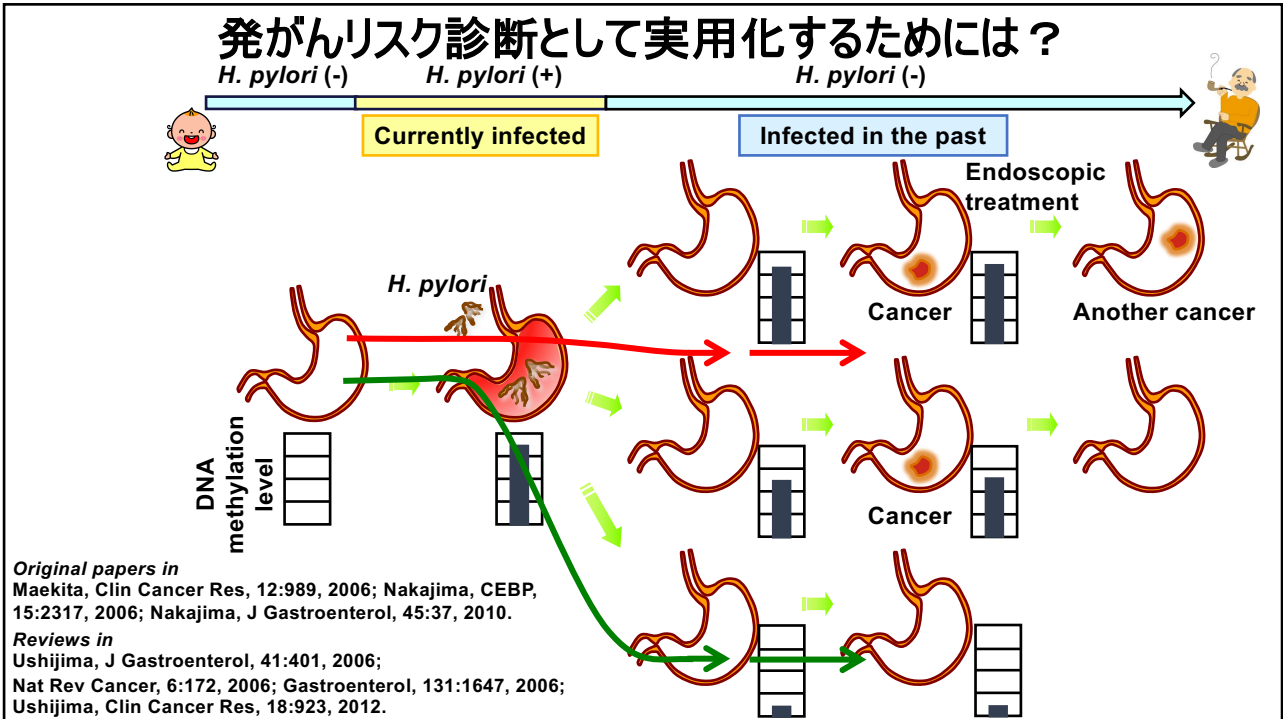
炎症によるメチル化標的遺伝子は若年者と高齢者で異なる

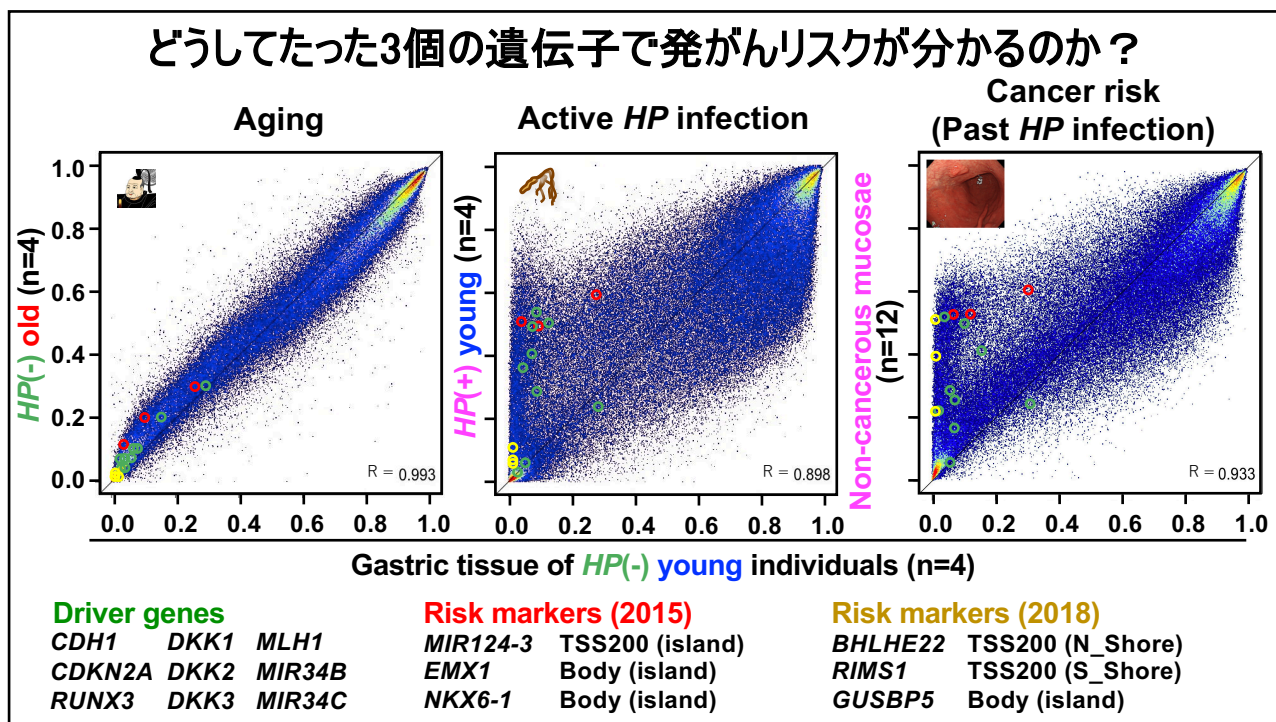
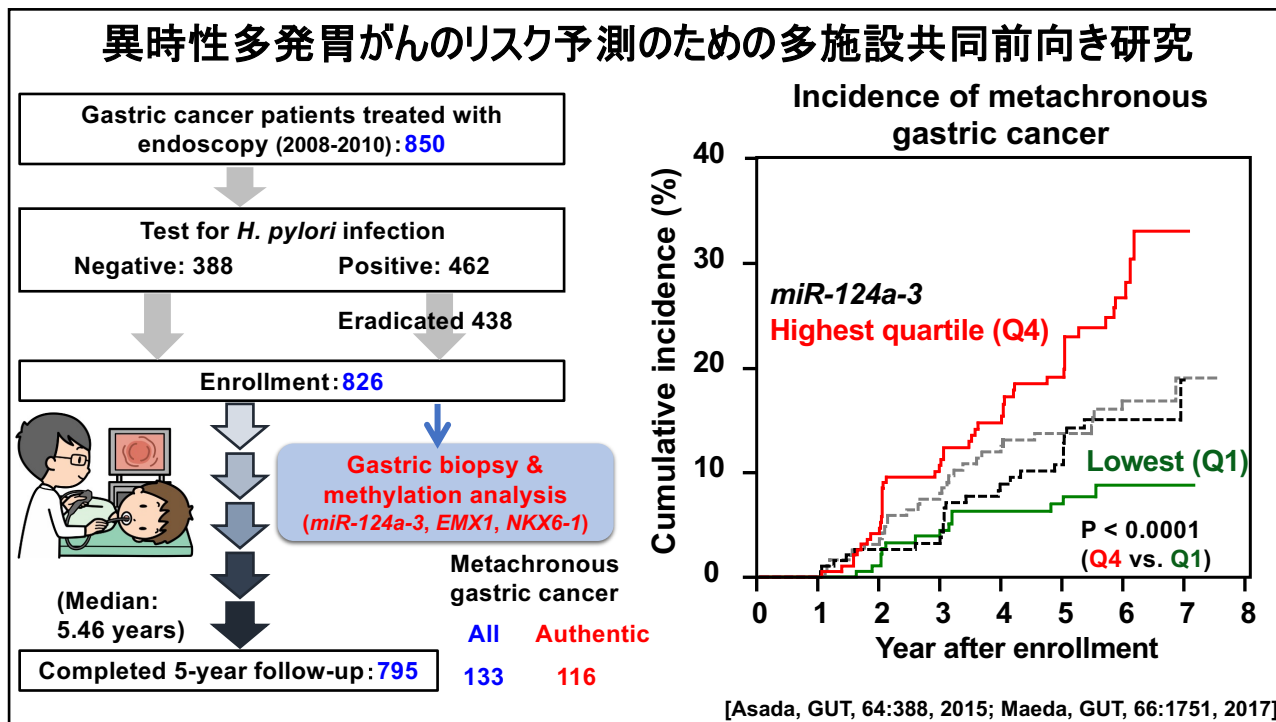


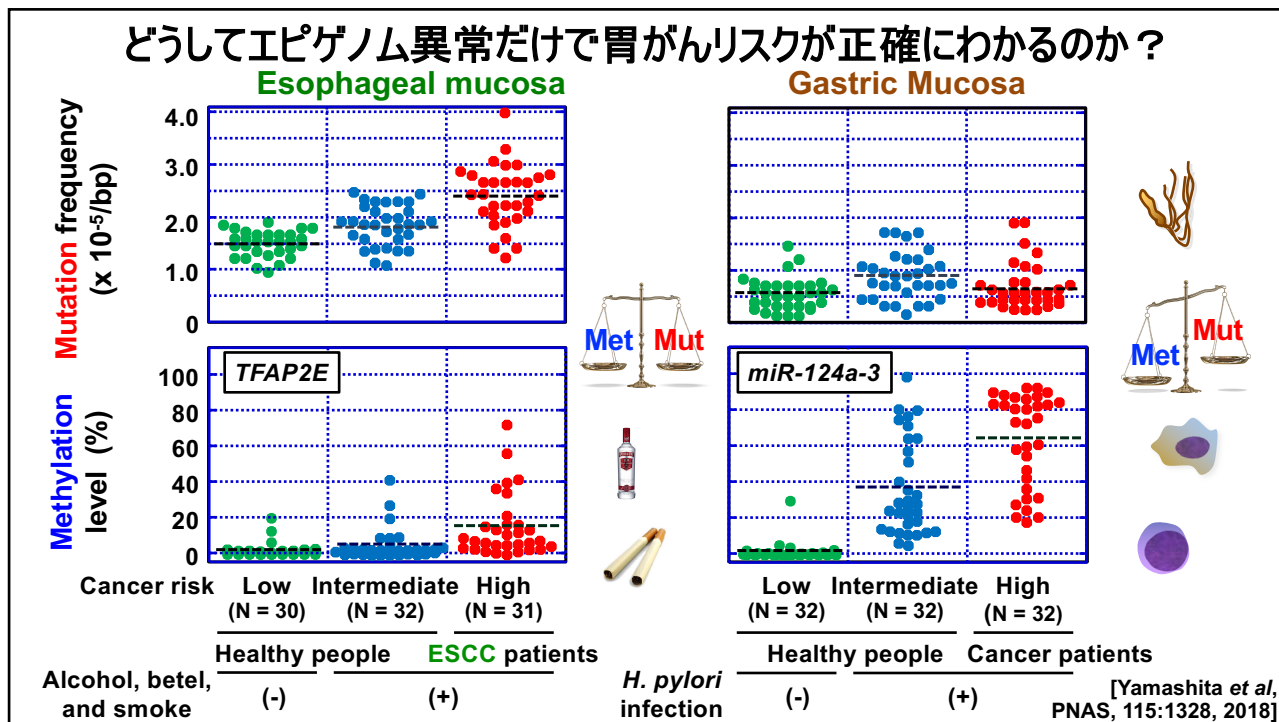
	 Age-related	 Inflammation-induced
Any genomic regions		
Basal methylation	needed	unnecessary
Promoter CpG islands		
microRNA	Frequent	Not
Gene expression	Only lowly expression	Even highly expressed

[Yamashita, Clin Epigenetics, 11:191, 2019]

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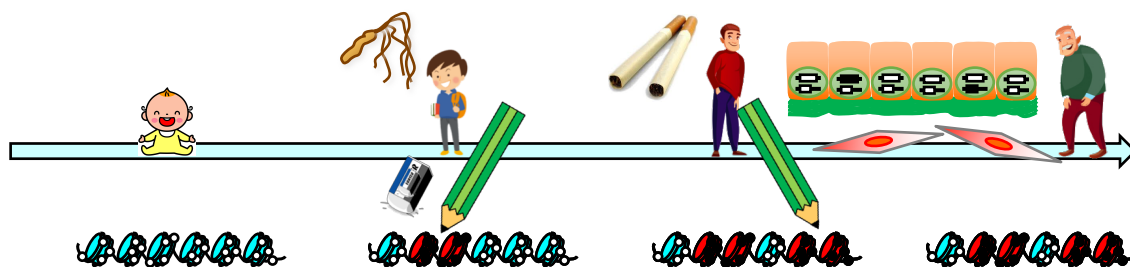






Conclusions

1. 正常組織に蓄積したDNAメチル化異常の量は発がんリスクと相関する。
2. NF- κ B活性化による *TET* の発現低下とNO産生によるDNMT活性上昇の悪い「食べ合わせ」はDNAメチル化異常を誘発する。
3. 慢性炎症は加齢ではメチル化されないようなゲノム領域・遺伝子のDNAメチル化異常を誘発する。
4. 組織に蓄積したDNAメチル化異常を用いて発がんリスクが診断できることが、多施設共同前向き臨床研究により示されている。



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Takahisa Furuta

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Hiroshima University

Tomoo Ito

Shiga University

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Nihon Medical University

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*NCC research and
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MEXT, Japan

