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·综　　述·

MAR 的分子结构

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Molecular Structure of Matrix Association Regions

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核基质(nuclear matrix)是真核生物细胞核中存在的主要由非组蛋白性纤维蛋白组成的空间网架结构。它参与了真核生物几乎所有的细胞核功能，包括 DNA 复制、RNA 的合成和调控以及 hnRNA 的加工、染色体的功能构建、有丝分裂、甾类激素作用、病毒复制和致癌作用等。最近的研究表明，核基质还与雌体细胞的第二条 X 染色体的钝化有关[1]。这些生物学功能是核基质通过识别基因组中与之特异结合的 DNA 序列——MAR(matrix association region)来实现的。自从 1984 年 Mirkovitch 等在果蝇 hsp70 和组蛋白基因侧翼发现第一批 MAR 分子以来[2]，已有大量的 MAR 在各种真核生物中被克隆和测序。作为真核染色质 loop 的边界元件(boundary elemnt)和染色质功能区域(fountional domain)的顺式作用元件[3]，MAR 为研究真核基因（或基因组）的结构和功能之间的对应关系提供了一种联系的纽带。表 1 中列出了截至 1997 年底所发现并鉴定的所有 MAR 分子，通过对这些 MAR 的序列分析，我们可以找到一些 MAR 的结构特征。

1 MAR 的分子结构特征

MAR 一般长约 100～1 000bp，但也有长达 7kb 的(如人 β 干扰素基因 5′上游的 MAR)。尽管 MAR 具有很多相似的一级结构特征，但不同的 MAR 分子之间并不能相互杂交[4]。通过比较 MAR 与来源于不同物种的核基质的体外结合能力，发现 MAR 与核基质的相互作用在进化上是高度保守的[5]。一般高等真核生物的每个细胞核中含有至少 10 000 个 MAR 分子和约 20 000 个 MAR 识别位点，这些位点由 MAR 结合蛋白组成，其中有一半可以识别单链 DNA，因此，认为 MAR 与核基质的相互作用在某种程度上基于核基质对单链 DNA 的识别[6]。

典型的 MAR 一般富含 AT(70%或以上)，主要由 A-box、T-box、ATATTT(T)序列以及与果蝇拓扑异构酶 II 位点(GTNA(T)AC(T)ATTNATNNA(G))相近的同义顺序等特征序列组成，其二级结构表现为狭窄的 DNA 小沟，易于弯曲和解链。

MAR 一般位于功能转录单位的侧翼，作为一种边界元件；但也有一些 MAR 位于某些基因的内含子中（如中国仓鼠 DHFR 基因、人类拓扑异构酶 I 基因、小鼠 Igκ 和 Igμ 基因），这些 MAR 可能主要是作为一种功能调控元件。

由于某一基因的染色体组织在进化上一般具有一定的保守性，如 *IgK* 基因内含子中的 MAR 在小鼠、兔和人类中都存在，而且具有很强的同源性。非洲爪蟾、大鼠和人类的 rRNA 基因都是成簇排列的，每个 rRNA 基因簇形成一个 DNA loop，它既是一个转录单位，也是一个复制单位和拓扑学限制性结构域[8]。理论上，在其

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他物种的 Igκ 基因或 rRNA 基因侧翼同样可能存在 MAR，因此以现有的一些 MAR 作为参照，我们可以对新发现的基因的调控和染色体组织进行研究。

2 MAR 结合蛋白(MAR-binding proteins)及其识别位点

由于核基质是一种人为制备的结构，对其在活体细胞中的结构、功能甚至存在性一直有争议。为了提供更有说服力的证据，人们开始把注意力转移到 MAR 结合蛋白上。只要找到某些蛋白，证明它们既可以和 MAR 紧密结合，又是核基质的组分，那么，这些 MAR 结合蛋白就是 MAR 与核基质相互作用的有力的间接证据。

表 1 目前已鉴定的 MAR 分子

时 间	来 源	侧翼基因(或位点)	MAR 数目	文 献
1984	Drosophila	histone gene repeat	2	2
		hsp70 gene (87A7 locus, 87C1 locus)	2	
1986	mouse	immunoglubulin κ light chain gene	1	4
	Drosophila	alcohol dehydrogenase gene	4	7
		Sgs-4 gene, Fushi taraza gene	4	
1987	mouse	immunoglubulin heavy chain gene	2	9
1988	Drosophila	region of rosy and Ace loci	2	10
		actin 5C gene	2	
	yeast	(HO, H4, HMR-E, 2μm plasmid) ARS, ARS1, CENIII, CENIV, CENXI	8	11
	human	β-interferon gene	3	12
		β-globin gene	1	13
		HPRT gene	1	14
	hamster	dihydrofolate reductase gene	2	15
1989	human	apolipoprotein B gene	3	16
1990	chicken	lysozyme gene	2	17
1991	tobocco	three root-specific tobocco genes	3	18
	chicken	α-globin gene 5′-end	1	19
		α-globin gene 3′-end	2	20
1992	murine	CD4 gene	2	21
	mouse	α-globin gene	1	22
1993	rat	glutamate-dehydrogenase gene	1	23
	human	embryo fibroblasts cDNA	1	24
	rat	osteocalcin gene	1	25
	rat	rDNA	2	26
	human	unknown	1	27
1994	yeast	ARS302, ARS3003	2	28
	human	γ-glubin gene	1	29
	puetunia	T-DNA integration site	1	30
	yeast	ARS307	1	31
1995	rat	carbomoylphosphate synthetase I gene	2	32
	maize	alcohol dehydrogenase1 gene	10	33
1996	human	HIV-1	1	34
		chromosome 19	8	45
	tomato	heat shock cognate 80 gene	2	36
1997	bean	β-phaseolin gene	2	37
	mouse	immunoglobin μ gene	1	38
	human	c-erbB-2 gene	1	39

目前已经纯化和鉴定的 MAR 结合蛋白共 10 余种（表 2）。包括核基质的重要组分 lamin B1、matrins、topoisomerase I&II、HMG I/Y(high mobility group nonhistone)、nucleolin；染色质的组分 histone H1；一些富含的特异蛋白，如 SATB1(special AT-rich binding protein)、ARBP(attachment region binding protein)、SAF-B(scaffold attachment factor B)、SAF-A/hnRNP U(heterogeneous nuclear RNP U)、nuclear scaffold

protein SP120、ACBP-67 / PAB1(polyA binding protein)(ARS consensus-binding protein)、ACBP-60 / PUB1 protein ssA-TIBF(single-strand A-rich type I repeat binding protein)；参与基因调控的反式作用因子，如 NF-muNR and MAR-BP1(nuclear factor-mu negative regulator)、osteocalcin gene's promoter-binding factors, NMP-1&2、HIV-NMP(nuclear matrix protein)；以及人工合成的 MATH(multi-AT hook) proteins。

表 2　MAR 结合蛋白及其识别位点的主要特征

MAR-binding proteins	识别的 DNA 序列或结构特征	文 献
lamin B_1	AT-rich MARs	40
matrins	AT-rich MARs	41
topoisomerase II	GTNA(T)AC(T)ATTNATNNA(G)	42
HMG I(Y)	narrow minor groove (AT-rich or GpC residue)	43
NMP-1&2	T(A)GT(C)GGT(AML-1 recognition motif)	44
SATB1	ATC sequences minor groove	45
ARBP	AT-rich DNA with motif of 5'-GGTGT-3'	46
SAF-B	AT-rich MARs	47
SAF-A / hnRNP U	MARs(>700bp), poly(G), ploy(I) or poly(U)	48
histone H_1	oligo(dA)· oligo(dT) (>130bp)	49
SP120	AT-rich MARs(>100bp)	50
ssA-TIBF	A-rich type I repeat	51
MATH proteins	AT-rich MARs	52
nucleolin	RNA, ssDNA, T-rich MARs, base-unpairing region	53
ACBP-67 / PAB1	A or T-rich single strand, ARS	54
ACBP-60	T-rich single strand, ARS	31
NF-muNR / MAR-BP1	AT-rich MARs	55
HIV-NMP	negative regulatory element of HIV-1 LTR	39

从表 2 中所列的 MAR 结合蛋白的识别序列，我们不难发现，一些组成性的 MAR 结合蛋白（如 lamin B1、matrins 以及 histone H1）主要识别富含 AT 的序列，而大部分蛋白则倾向于识别 MAR 的二级结构，如小沟、弯曲和解链区。富含 AT 的 DNA 并不一定就是 MAR，一些 AT 含量较低的 DNA 序列由于具有 MAR 的二级结构特征而可以与核基质特异性体外结合。

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