ence, development of scientific institutions, linkages between research and industry and on computers and electronics, brought out many similarities between the experiences in the two countries. The importance of strong, individual leadership in inspiring a line of research scholars and establishing stable traditions—with the vitality to produce new leaders in diversified fields—was emphasized. In both the countries in the post-war period, new multidisciplinary centres for scientific R&D had to be established, independent of the existing universities and some of them were devoted to specific mission programmes with substantial Government funding (e.g. atomic energy, space, defence). However, in France, over a period of time, the need to again reinforce the university system has come to be recognized. Basic research flourishes better when associated with teaching responsibilities and in the environment of young graduate research students. At the same time, it has not been easy to transfer the results of university laboratory research to industrial practice for commercialization, and it has been felt that applied research is best pursued in the environment of the industry. In both the countries, so far, electronics has grown mainly in the industrial sector, without the establishment of a multidisciplinary centre of excellence (unlike in the case of atomic energy and space).

The tendency to publish the best scientific work outside is common to both the countries, to the detriment of the quality of local journals. While France contributes to some 7–10% of the world scientific output, only 1% gets published in French journals. Out of a total of 1500 science journals in France, only about 150 are rated as good quality.

In the valedictory session, in which among others the French Minister for Science, Hubert Curien, and the Indian Minister for Science and Technology, Rangarajan Kumaramangalam participated, genuine hope was expressed in implementing effective exchange programmes in areas of mutual interest. In particular, Curien commended the possibility of twin programmes at chosen centres on both sides.

An important reference was made by Curien to the rise of 'anti-science', 'anti-technology' movements in several parts of the world, including France. He said that it has become all the more necessary for the scientists to make science not only 'meaningful' but also 'attractive' to the general public.

Science will grow on the inner compulsions of scientific curiosity and on the sound base of intellectual integrity and objectivity. Science is increasingly needed to find new pathways for human progress. For the public to support scientific activity in adequate measure, the techniques of communication have to be vastly improved, in an atmosphere of mutual trust and respect.

Bhargava and Balibar deserve to be congratulated for their initiatives in composing a balanced programme and ensuring the participation of experienced scientists from both sides, and for the keen involvement with which they conducted the proceedings. It is proposed to bring out the Proceedings of the Seminar as a UNESCO publication.

Science is not produced in a vacuum by disembodied minds and pure intellects, and its production should not be characterized only, or even primarily, as a debate between the individual and 'Nature'. Scientific activity is a collective endeavour which requires, to exist, a shared set of cultural values, of social commitments, of procedures of legitimation, of institutions; it is a social enterprise which requires a set of practical and intellectual rules. Each of those sets, which varies according to places and from one period to another, defines what could be called the system, or the regime, of a science at a given moment in a certain place.

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RESEARCH NEWS

Inheritance of chromatin structure: DNA methylation and other means

Rakesh K. Mishra

DNA methylation has been proposed to play an important role in gene inactivation, genomic imprinting, dosage compensation by X-inactivation, carcinogenesis, ageing, etc. in mammals. However, such propositions have been largely based on correlative and indirect evidence and hence are a subject of debate[1]. Further, the absence of DNA methylation at any stage in the life-cycle of well-studied systems, viz. Drosophila, Coenorhabditis and yeasts, raised questions about the relevance of methylation of DNA and its involvement in very basic processes which otherwise seem to have many generalities and parallels.

The recent report by Li *et al.*[2] puts to rest the debate on the importance of DNA methylation in mammals. Their study demonstrates that mutation in methyl transferase, the only known gene responsible for methylation of CpG islands in mammals, is recessive lethal as the embryos homozygous for the mutation in this gene have retarded initial development and die before the 11-day stage. Such embryos show only 30% of the overall methylation compared to the wild-types. This report, hence, unequivocally establishes the essentiality of DNA methylation during early embryonic development, at least in mouse. It has been shown previously

that overall level of methylation in embryonic, extra embryonic and germ cell lineages changes in a temporal and region-specific manner during the development of mouse embryo[3]. In a recent study, Kafri *et al.*[4] report results on similar lines using more sensitive method in a systematic manner. Figure 1 shows this dynamic nature of DNA methylation along different stages of cellular *differentiation. Taking into account* these results along with the view that methylation is potentially involved in epigenetic inheritance and the report of Li *et al.*, it becomes apparent that low methylation represents undifferentiated or pluripotent cells and more methylated DNA, differentiating or differentiated cells. This suggests that during mouse development, after the initial pattern is established by the transient expression of differentiation regulatory genes, the methylation is probably used in a critical manner to remember and inherit the differentiated state of chromatin organization.

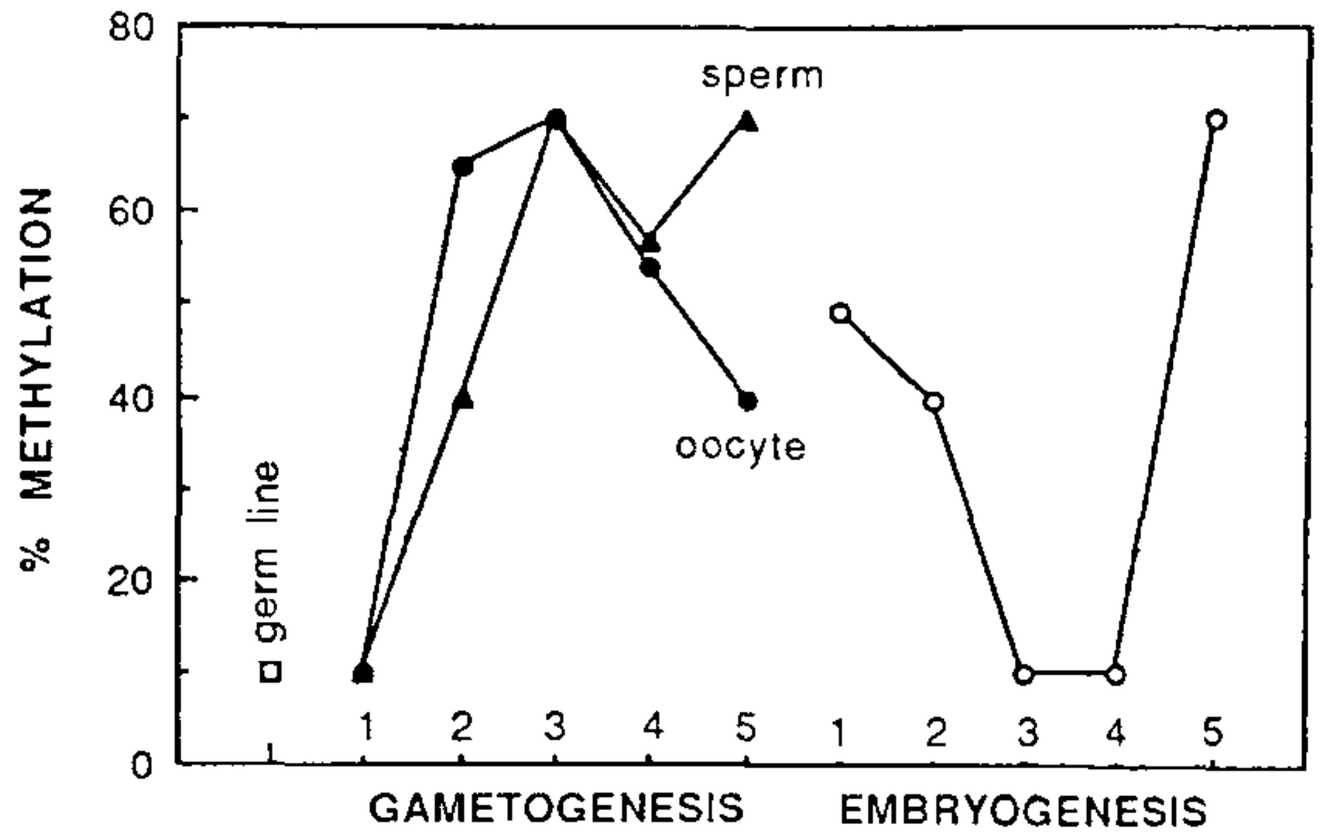

Figure 1. Change in the extent of DNA methylation along the cellular differentiation in mouse. In gametogenesis 1–4 represent 13 5, 15 5, 18 5 and 21 5 day (or spermatogonia) stages respectively In embryogenesis 1–5 represent 4 cell, 8 cell, 16 cell, blastocyst and 6 5 day stages respectively. The level of methylation is averaged from several loci and represents a relative and qualitative picture (for a more detailed analysis see ref. 4).

In Drosophila, during early development the embryo is divided into fourteen parasegments. The identity of each parasegment is established by an intricate and precise pattern of homeotic gene expression, determined by the transient expression of early differentiation genes, called segmentation genes (comprised of gap genes, pair-rule genes and segment polarity genes)[5]. This differentiated state is maintained by the balance of the activity of two sets of genes called Trithorax and Polycomb group, PcG, of genes. In the absence of PcG genes the initial pattern of development is normal but embryo shows ectopic expression of homeotic genes at later stages, finally leading to lethality[6]. This indicated the role of these genes in maintaining the differentiated pattern of chromatin organization by specific repression of unwanted genes in a lineage-specific manner through cell division. Pc shares homology to HP1, a member of the group of genes belonging to the modifiers of position effect variegation (PEV). Interestingly, some PcG genes have been shown to influence PEV and also some modifiers of PEV display homeotic transformation upon mutation[7]. It has been suggested that these families of genes encode non-histone structural components of chromatin and bring out global regulation of genes by formation of multicomponent nondiffusible mega-complexes on chromatin in dosage-dependent manner[8–11]. Such patterns are required to be clonally inheritable through cell division. Epigenetic inheritance of repressed state of Mating Type (MAT) locus in yeast through such structural means has been proposed before[12].

The comparison of the PcG genes and the DNA methylation reveals a neat parallel. Both are involved in the maintenance of chromatin structure during cell division. Incidentally, both are present as maternal contribution and are produced zygotically subsequently. That may be the explanation why mutant embryos show even the extent of development observed in both the cases. Figure 2 presents a general scheme of this parallel. From a functional point of view, therefore, PcG genes and methyl transferase are equivalent. Both the functions mark inactive stretches of chromatin and maintain them so during the life-cycle of the organism by mechanisms[13,14], which may be thematically similar but different in molecular details and are an exciting subject for future investigations. This proposition provides functional substitute of methylation in Drosophila. However, methylation and PcG genes may not be mutually exclusive and it is likely that the multicomponent structural core provided by PcG proteins may be utilized as hardware in mammalian chromatin as well. Indeed, Pc homologues in mammal have been already found[15].

Molecular analysis of several genetic loci related to PcG or enhancers or supressors of PEV will be useful in understanding the molecular aspects of higher order chromatin structure and function. It is, however, crucial to understand what kind of *cis* elements serve as the boundaries of such structures on the chromosomes. The boundaries of the chromatin 'domains' are the obvious candidates but the interesting question

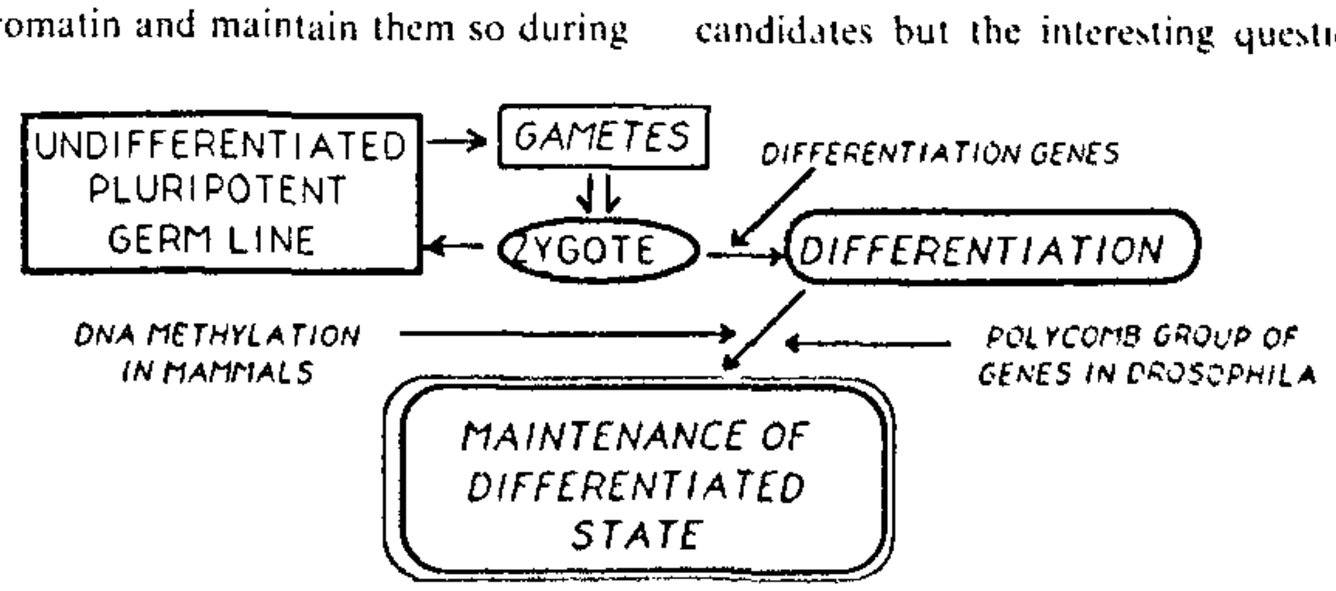

Figure 2. A model for the functional equivalence of methylation and PcG genes in maintenance of differentiated chromatin structure

that emerges is whether there are several kinds of boundaries. For instance, a kind of boundary may mark start or end of the heterochromatin stretch in a directional fashion while other kind may include weaker boundaries within an active or inactive stretch which may respond to more subtle regulatory mechanisms. With the availability of an *in vivo* boundary assay system and several mutations related to such boundaries[16], it may not be too distant a future when such questions will be answered.

Inactivating and or maintaining regions of genome by means of methylation (in mammals) by a set of chromosomal proteins (in fruit fly) or by elimination of stretches of DNA itself (in ascaris) shows that organization of the genome (including repetitive DNA) has evolved in parallel with the corresponding mechanisms to meet the complex genetic obligations of somatic differentiation and germ line totipotency. It is notable that during evolution as the species have digressed they have built upon one mechanism or the other leading to a common goal, viz. to have genetic information for a mechanism to unfurl the developmental programme in the majority of cells which may or may not be reversible, while maintaining the blue-print in the germ line for the progeny.

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Rabid roles in vesicle fusion

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Rab proteins are members of the ras superfamily of family of GTP-binding, peripheral membrane proteins; rab proteins regulate the fusion of intracellular transport vesicles. Bowser *et al.* report[1] the sequence of a protein likely to associate with a member of the rab protein family during vesicle fusion. In addition, it adds to the growing number of identified cytosolic proteins involved in fusion of intracellular transport vesicles.

Studies on various membrane traffic pathways have revealed that rab proteins are required for the fusion of a wide range of transport vesicles. Each vesicle type is believed to be associated with a specific rab protein; molecules governing this specific association are unknown. As target specificity and vectoriality are salient features of vesicle fusion[2], considerable effort has been focused on identifying proteins that interact with rabs; such associated proteins are candidates for specific markers of donor or target membranes, potentially involved in bio-genesis and function of transport vesicles. It is fitting that the first rab-associated protein involved in vesicle fusion may have been identified for the *sec4* protein of *S. cerevesiae*, the first member of the rab family to be described[3]. The rab-associated protein is sec8p, a protein also required for fusion of secretory vesicles with plasma membrane. Its association with sec4p is argued from genetic interactions, *sec4–8*, *sec8–9* double mutants show synthetic lethality, and a duplication of *sec4* partially suppresses a temperature sensitive (ts) mutation in *sec8*; from biochemical association studies, a portion of intracellular sec4p is found in a protein complex that contains sec8p and sec15p (yet another late-acting sec protein); and from sequence analysis of *sec8* that shows weak but recognizable similarity to a non-catalytic domain of adenylate cyclase required for responsiveness to ras regulation.

Sec8p is hydrophilic and only peripherally associated with plasma membrane. Thus, the identification of sec8p as a potential sec4p-binding protein, does not constitute a major advance in the question of target recognition by secretory vesicles. It remains unclear how sec4p associates specifically with secretory vesicles and sec8p with plasma membrane. It is yet unproven that the binding of vesicular sec4p with membrane sec8p is a primary event in target recognition; also unresolved is whether this binding stimulates a GTPase activity of sec4p that has been postulated to accompany vesicle fusion. However, since rab proteins are key components for function of transport vesicles, the identification of proteins that interact directly with sec4p constitutes a significant advance. It is possible that new families of sec8p and sec15p homologs that interact with different rab proteins may be involved in the function of varied transport vesicles.