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# Molecular aspects of retinoic acid receptor function in mouse ES cell differentiation

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All trans-retinoic acid (RA), the naturally active vitamin A metabolite exerts a wide range of effects on vertebrate development and adult tissue homeostasis by regulating cell proliferation, differentiation and apoptosis. RA acts through Retinoic Acid Receptors (RARs) that bind RA response elements (RAREs) in regulatory regions of their target genes. While canonical RAREs comprise direct repeats of the consensus 5¹-RGKTCA-3¹ separated by 1, 2 or 5 nucleotides (DR1, 2, 5), we show that shortly after RA treatment of mouse embryoid bodies or F9 cells, RARs occupy a large repertoire of predominantly DR0, DR8 and IR0 elements. In vitro, RAR-RXR binds these non-canonical spacings with comparable affinities to DR2 and DR5. Most DR8 elements comprise three half sites with DR2 and DR0 spacings. This specific half site organization constitutes a previously unrecognized, but frequent signature of RAR binding elements and acts as an RARE. At later stages of embryoid body differentiation, RARs relocalise to a restricted repertoire of sites comprising predominantly DR5 elements. Differentiation thus involves genomic relocalisation of RARs, and a switch from DR0 and DR8 at early times to DR5 at later stages.

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