Dimethyl Sulfoxide Affects the Selection of Splice Sites*

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Depending on the cell line and cell types, dimethyl sulfoxide (Me2SO) can induce or block cell differentiation and apoptosis. Although Me2SO treatment alters many levels of gene expression, the molecular processes that are directly affected by Me2SO have not been clearly identified. Here, we report that Me2SO affects splice site selection on model pre-mRNAs incubated in a nuclear extract prepared from HeLa cells. A shift toward the proximal pair of splice sites was observed on pre-mRNAs carrying competing 5′-splice sites or competing 3′-splice sites. Because the activity of recombinant hnRNPs A1 protein was similar when added to extracts containing or lacking Me2SO, the activity of endogenous A1 proteins is probably not affected by Me2SO. Notably, in a manner reminiscent of SR proteins, Me2SO activated splicing in a HeLa S100 extract. Moreover, the activity of recombinant SR proteins in splice site selection in vitro was improved by Me2SO. Polar solvents like DMF and formamide similarly modulated splice site selection in vitro but formamide did not activate a HeLa S100 extract. We propose that Me2SO improves ionic interactions between splicing factors that contain RS-domains. The direct impact of Me2SO on alternative splicing may explain, at least in part, the different and sometimes opposite effects of Me2SO on cell differentiation and apoptosis.

Me2SO is a polar solvent used to promote cell differentiation of tumor cell lines. For example, the treatment of mouse erythroleukemic and neuroblastoma cells with 2% Me2SO induces morphological changes and differentiation in red blood cells and neurons, respectively (e.g. see Refs. 1, 2). Me2SO also induces differentiation of the human U937 monoblast leukemia cell line into monocyte/macrophage (3) and stimulates the differentiation of a human ovarian adenocarcinoma cell line (4). Paradoxically, Me2SO prevents the terminal differentiation of myoblasts (5, 6), inhibits the differentiation of adipocytes (7), blocks the differentiation of antibody-producing plasma cells (8), and interferes with the differentiation of chick embryo chondrocytes (9). Whereas Me2SO has been used to induce apoptosis in some cell lines (10, 11), it inhibits cell density-dependent apoptosis of CHO cells (6). Thus, depending on the cell line, Me2SO can have completely different effects on differentiation and apoptosis.

The cellular mechanisms that are affected by Me2SO remain unclear. Because Me2SO facilitates DNA uptake during transfection procedures (e.g. see Ref. 12), Me2SO has been proposed to affect the integrity of cell membranes. Because Me2SO alters protein kinase C activity and the expression of integrin complexes (6, 13), Me2SO may alter intracellular signaling processes, which in turn may have a broad impact on many aspects of gene expression. Me2SO treatment promotes changes in the abundance of certain mRNAs and in the ratio of spliced isoforms (14–17). Among the genes reported to be affected in their alternative splicing is the NCAM pre-mRNA. A 2% Me2SO treatment of N2a cells promotes an increase in the inclusion of neuro-specific NCAM exon 18 (18, 19). Me2SO alters the alternative splicing of other genes including the amyloid precursor protein (20), the serotonin 5-HT3 receptor-A mRNA (21), and p53 (22, 23). Me2SO has also been associated with an effect on c-Myc mRNA elongation, maturation, and stability (23–25), and on the translation of some mRNAs (1). Whether any of the above changes result from a direct effect of Me2SO on RNA synthesis, maturation, and/or stability is currently unknown.

Because treating cells with Me2SO can have a strong effect on the alternative splicing of many pre-mRNAs and because the mechanism of action of Me2SO remains unclear, we performed a series of experiments in nuclear extracts to assess whether Me2SO directly affects the activity of the splicing machinery. We find that Me2SO can have drastic effects both on 5′-splice site and on 3′-splice site selection in vitro. Notably, other solvents of the same category (e.g. DMF and formamide) also perturb splice site selection.

EXPERIMENTAL PROCEDURES

Treatment of Cells with Me2SO and in Vivo Alternative Splicing Assays—Me2SO was purchased from various suppliers including EM Science and Fisher Scientific Inc. DMF and formamide were from Calbiochem. N2a and HeLa cells were cultured at 37 °C in Dulbecco’s modified Eagle’s medium supplemented with 10% bovine calf serum. For treatment with Me2SO, medium containing 2% bovine calf serum was used. Following treatment, total RNA was isolated using the guanidinium-HCl protocol as described in Chabot (26). RNase T1 protection assay was performed according to Melton et al. (27) using a uniformly labeled 530-nt NCAM antisense RNA probe. Exon 17/exon 19 splicing yields a 303-nt protected fragment while the inclusion of exon 18 produces a 452-nt fragment. Products were resolved on a 5% denaturing acrylamide gel. The reverse transcriptase-PCR assay used to amplify products corresponding to exon 7B inclusion and exclusion has been described in Chabot et al. (28).

Substrate Pre-mRNAs and in Vitro Splicing Assays—pC5′–/–, pC5′/4′ and pC3′–/– have been described in Blanchette and Chabot (29). pNCAM3′ was constructed by substituting the 3′-splice site of exon 7B
Dimethyl Sulfoxide and Splice Site Usage

RESULTS

Me2SO Affects Alternative Pre-mRNA Splicing in Vivo—Me2SO can promote cell differentiation, a process that is often associated with a change in the alternative splicing profile of specific genes. One example of this effect is found in the mouse N2a neuroblastoma cell line. The treatment of N2a cells with 2% Me2SO induces neuronal cell differentiation and improves the frequency of inclusion of the neurospecific exon 18 in the NCAM pre-mRNA (Refs. 2, 31; Fig. 1A). A similar effect was observed on the hnRNP A1 pre-mRNA. In this case, we monitored the inclusion frequency of alternative exon 7B following the treatment of HeLa cells for 5 h with 5% Me2SO (Fig. 1B). Although the effect was less dramatic than for the NCAM pre-mRNA, Me2SO treatment significantly improved the inclusion of exon 7B.

Me2SO Affects Splice Site Selection in Vitro—To determine whether Me2SO can modulate splice site selection directly, we tested the effect of adding Me2SO to splicing reactions incubated in nuclear extracts prepared from HeLa cells. We used model pre-mRNAs derived from the hnRNP A1 alternative splicing unit (29). C5\' \(-/-\) contains two competing 5'-splice sites and a unique 3'-splice site (Fig. 2A). C5\' \(-/-\) is spliced almost exclusively to the proximal 5'-splice site (Fig. 2B, lane 1). In contrast, the presence of A1 binding elements in C5\' 4/4 promotes efficient splicing to the distal 5'-splice site (lane 5). The addition of Me2SO at a final concentration of 0.8, 1.6, and 2.4% did not affect the splicing efficiency of C5\' \(-/-\) RNA, and 5'-splice site selection remained exclusively proximal (Fig. 2B, lanes 2–4). In contrast, Me2SO promoted a strong reduction in the use of distal 5'-splice site in C5\' 4/4 pre-mRNA (lanes 6–8).

The highest concentration of Me2SO (lane 8) produced a 5-fold decrease in the use of the distal 5'-splice site. In some experiments, the reduction in distal 5'-splice site usage was accompanied by an increase in the production of lariat products derived from the proximal 5'-splice site (e.g. see Fig. 5A, lane 2). The effect of Me2SO on 5'-splice site selection was as strong on a pre-mRNA that was synthesized in the absence of cap analogue (data not shown). Thus, the reduction in distal 5'-splice site usage was independent of the cap structure at the 5'-end of the pre-mRNA. Me2SO also affected 5'-splice site...
selection in a model pre-mRNA carrying two copies of the 5'-splice site of exon 7 (data not shown). Identical effects were seen with Me₂SO solutions obtained from different suppliers, and the deionization of Me₂SO did not change its activity on 5'-splice site selection (data not shown). Transient exposure of nuclear extracts to Me₂SO (i.e., incubation in the presence of Me₂SO followed by dialysis) did not affect 5'-splice site usage (data not shown). Thus, Me₂SO needs to be present in splicing mixtures to affect splice site selection.

Because Me₂SO had a strong effect on the alternative splicing of a pre-mRNA carrying A1 binding elements (C5 4/4), we asked whether Me₂SO compromised the activity of the hnRNP A1 protein. We have shown previously that hnRNP A1 promotes distal 5'-splice site utilization on this pre-mRNA (29). In nuclear extracts containing Me₂SO, the addition of hnRNP A1 efficiently shifted selection toward the distal 5'-splice site (Fig. 3A, lanes 6–10). The effect was specific because the addition of similar amounts of GST or gene 32 protein had no effect (data not shown). Notably, the profile of selection obtained with increasing amounts of recombinant A1 was similar to the profile obtained in a nuclear extract lacking Me₂SO (Fig. 3A, lanes 1–5; compare the slopes in Fig. 3B). Because the activity of recombinant hnRNP A1 is not compromised by the presence of Me₂SO, it is unlikely that Me₂SO affects the activity of the endogenous A1 proteins.

To address whether Me₂SO has a similar activity on 3'-splice site selection we tested a pre-mRNA (C3' 4/4; Fig. 4A), which is spliced predominantly to the distal 3'-splice site (Ref. 29; Fig. 4B, lane 1). C3' 4/4 splicing was sensitive to increasing amounts of Me₂SO (Fig. 4B, lanes 2–4). At the highest concentration of Me₂SO (lane 4), more than 50% of splicing occurred at the proximal 3'-splice site. We also tested a derivative of C3' 4/4 in which the central portion was substituted for the 3'-splice site region and a portion of NCAM alternative exon 18 (NCAM3' RNA). Although splicing of NCAM3' RNA was less sensitive to Me₂SO than C3' 4/4, Me₂SO promoted a stronger reduction in the use of the distal 3'-splice site than of the proximal 3'-splice site (Fig. 4B, lanes 5–9). Alternative splicing of a β-globin pre-mRNA carrying duplicated 3'-splice sites was also affected by Me₂SO (data not shown).

Me₂SO Activates SR Proteins—The effect of Me₂SO on splice site selection is reminiscent of the activity of SR proteins, which tend to activate splicing of the proximal pair of splice sites (32, 33). Although Me₂SO did not stimulate overall splicing activity in nuclear extracts (Fig. 5A, lanes 1 and 2), we asked whether Me₂SO could mimic the generic splicing activity of SR proteins. This activity was initially defined by the capacity of SR proteins to activate splicing in a HeLa S100 extract, either as a mixture of SR proteins or individually (33, 34). U2AF₆₅ also activates splicing when added to a HeLa S100 extract (35). Notably, the addition of Me₂SO to a HeLa S100 extract stimulated splicing as efficiently as the addition of the recombinant SR protein ASF/SF2 (Fig. 5A, lanes 3–5). The
addition of Me₂SO to a S100 extract also stimulated the formation of complexes, as judged by native gel analysis (Fig 5B, lanes 7–9). These results suggest that Me₂SO increases the activity of residual amounts of SR or U2AF proteins in the S100 extract. The level of splicing variation spread considerably in different preparations of S100 extract. Although Me₂SO and recombinant ASF/SF2 restored splicing activity in a similar manner, splicing to the distal 5′-splice site was not detected, as is the case in a nuclear extract (lanes 1 and 2). We have shown previously that distal 5′-splice site selection on this pre-mRNA requires hnRNP A1 (29). The failure to activate distal 5′-splice site use is probably because of the fact that S100 extracts contain small amounts of hnRNP A/B proteins as compared with nuclear extracts (not shown).

The above result suggests that Me₂SO may affect the activity of SR proteins. To further examine this possibility, we tested the effect of adding Me₂SO to splicing reactions preincubated with a recombinant SR protein. At the concentrations used and in the absence of Me₂SO, the recombinant SR protein GST-SRP30c had little effect on 5′-splice site selection when using the C5′ 4/4 pre-mRNA (Fig. 6A, lanes 1–3). However, in the presence of Me₂SO, the same amount of GST-SRP30c stimulated proximal 5′-splice site utilization (lanes 4–12). Thus, the simultaneous addition of Me₂SO and SR produced a shift toward proximal use that was greater than the sum of their individual contributions. Because recombinant SR proteins display more activity in the presence of Me₂SO, a similar effect on the endogenous SR proteins may be responsible for the activity of Me₂SO in nuclear extracts.

**DISCUSSION**

We have observed that the addition of Me₂SO to nuclear extracts can have strong effects on splice site selection while having minimal effects on the efficiency of splicing. In contrast, the addition of Me₂SO to a splicing-deficient HeLa S100 extract stimulated splicing in a manner reminiscent of the activity of SR proteins. The effect of Me₂SO on splice site selection was also similar to the activity of SR proteins because Me₂SO shifted selection toward the proximal pair of splice sites. Consistent with the notion Me₂SO stimulates the activity of SR proteins, we found that the combination of Me₂SO and SRp30c produces a shift that is greater than the sum of their individual contribution. Thus, a general stimulation in the activity of all endogenous SR proteins most probably explains why Me₂SO influences splice site choice in vitro. Likewise, the addition of Me₂SO to a S100 extract may stimulate the residual amounts of SR proteins present in this extract.

An additional mechanism by which Me₂SO may affect splice site selection is through the inactivation of the hnRNP A/B proteins, which are known to antagonize the activity of SR proteins in splice site selection (36, 37). However, we have
observed that the activity of recombinant hnRNP A1 proteins in splice site selection is not affected by the presence of Me₂SO. This result suggests that the activity of endogenous A1 proteins is probably not affected by Me₂SO.

Because Me₂SO, DMF, and formamide decrease the melting temperature of DNA and RNA duplexes, it is possible that changes in 5′-splice site selection may be caused by the weakening of the base pairing interactions between U1 snRNA and 5′-splice sites. However, this explanation is unlikely for the following reasons. First, a reduction in U1 snRNP binding should lead to more distal 5′-splice site utilization, as is the case when U1 activity is reduced through oligonucleotide-targeted RNase H digestion (data not shown). Moreover, increased selection of a proximal 5′-splice site is associated with improved U1 snRNP binding (38). Second, splice site selection on a transcript that is normally spliced to a distal 5′-splice site because of a duplex structure in the pre-mRNA was insensitive to Me₂SO. Thus, the effect of Me₂SO, formamide and DMF on 5′-splice site selection cannot be explained by a reduction in the stability of base pairing interactions. However, it is possible that this denaturing activity contributes to the reduction in overall splicing activity observed at higher concentrations of solvents.

Although our results suggest that Me₂SO affects the activity of SR proteins, the mechanism by which SR proteins become activated remains unclear. Western analysis using an antibody that recognizes phosphorylated epitopes on SR proteins revealed no change in the overall and relative abundance of phosphorylated SR proteins upon incubation with Me₂SO (data not shown). Moreover, Me₂SO did not affect the binding of SR proteins to a purine-rich RNA splicing enhancer element (data not shown). Me₂SO also did not modify the solubility of SR proteins when extracts were incubated with increasing concentrations of MgCl₂ (data not shown). Although Me₂SO is regarded as a relatively inert solvent for pharmacological applications, it improves the solvation of cations and stimulates nucleophilic reactions. DMF and formamide share with Me₂SO this chemical property. Thus, one possibility is that Me₂SO improves the solvation of positive charges on proteins. This may influence the structure at the surface of proteins and facilitate ionic contacts between charged domains of interacting proteins. Consistent with this view, modulation of 5′-splice site selection in vitro is known to be sensitive to the ionic conditions of the reaction (39). Splicing proteins that carry charged domains include SR and U2AF proteins, which have RS-domains rich in positively and negatively charged amino acids (arginines and phosphorylated serines, respectively). Interactions between the RS-domain containing proteins ASF/SF2, U1 snRNP-70 kDa, and U2AF35 have been proposed to occur early during spliceosome assembly (40). Moreover, these interactions are sensitive to the phosphorylation state of ASF/SF2 (41). Thus, Me₂SO may activate splicing in a S100 extract by improving the quality of the ionic interactions between residual amounts of SR and U2AF proteins. Because the amount and activity of these proteins are in excess in a nuclear extract, this would explain why Me₂SO stimulates generic splicing in a S100 but not in a nuclear extract.

Even though nuclear extracts contain sufficient amounts of SR proteins for generic splicing, their activity in splice site selection is not maximal because adding more SR proteins can have a strong effect on the selection of splice sites (32, 33). Because a similar effect can be obtained by adding kinases that phosphorylate the RS domains of SR proteins (42), the profile of charged residues at the surface of SR proteins is crucial for their activity as splicing regulators. Moreover, the requirement for charged residues at the surface of SR proteins appears different for generic and alternative splicing because dephosphorylation of ASF/SF2 is essential for constitutive splicing, but is not required for the protein to function as a splicing regulator (41). Thus, Me₂SO may affect the presentation of charged residues that are important for the activity of SR proteins in splice site selection. Because Me₂SO and DMF activate splicing in a HeLa S100 extract, Me₂SO and DMF may also affect the presentation of different residues that are important for generic splicing. In contrast, because formamide affects splice site selection but cannot activate a S100 extract, formamide may only affect the presentation of residues that play a role in splice site selection.

Our results raise the possibility that the documented effect of Me₂SO on cell differentiation may be caused, at least in part, by changes in the activity of SR proteins, which in turn affect splice site selection. This conclusion is supported by the observation that DMF can mimic the effect of Me₂SO both in differentiation assays (5, 43–45), and in splicing assays in vitro. Depending on the cell types, Me₂SO can either promote or block differentiation or apoptosis. These opposite outcomes may be explained if different subsets of pre-mRNAs are expressed in different cell types. For example, alternative splicing is often used to control the production of proteins involved in programmed cell death such as Fas, Bcl-2, Bax, and Ced-4 (46). Hence, Me₂SO may alter the alternative splicing of a pre-mRNA to favor the production of a repressor protein in one cell type, while an inducer may be produced from another gene in a different cell type.
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