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14. Myocyte shortening was measured by projecting the image of the cell edge on a linear 256-element photodiode array. The position of the cell edge was determined at 4-ms intervals and converted into absolute changes in cell length. The output signal was filtered at 500 Hz.
15. For measurement of intracellular Ca^{2+} transients, cells were loaded with fura-2 (pentapotassium salt) via the pipette. A mirror oscillating at 1.2 kHz was used as a mechanical light chopper for dual wavelength excitation at 330 and 410 nm. Fluorescence emission was measured at 510 nm. Details are given in (*6*).
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24. A 2-nA Ba^{2+} current flowing for the duration of a 200-ms clamp pulse will add 2 fmol [2 nA × 0.2/(2 × Faraday constant)] to an intracellular volume of 20 pl (10 μm × 20 μm × 100 μm), thereby changing the total intracellular Ba^{2+} concentration by 2 fmol/20 pl or 100 μM. Thus Ba^{2+} will bind to a significant fraction of the troponin C and fura-2 molecules.
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Induction of Mesoderm by a Viral Oncogene in Early *Xenopus* Embryos

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During frog embryogenesis, mesoderm is specified in the equatorial region of the early embryo by a signal from the vegetal hemisphere. Prospective ectodermal cells dissected from the animal hemisphere can be respecified to form mesodermal tissues by recombination with vegetal tissue or by treatment with any of several polypeptide growth factors or growth factor–like molecules. Together with the discovery that several developmental mutations in *Drosophila* are in genes with significant homology to mammalian mitogens and oncogenes, these observations suggest that early developmental signals may use similar transduction pathways to mitogenic signals characterized in cultured mammalian cells. Whether mesoderm can be induced by activation of intracellular signal transduction pathways implicated in mitogenesis and oncogenesis has been investigated with the viral oncogene polyoma middle T. Microinjection of middle T messenger RNA into early embryos results in the respecification of isolated prospective ectodermal tissue to form characteristic mesodermal structures. Middle T in frog blastomeres appears to associate with cellular activities similar to those observed in polyoma-transformed mouse cells, and transformation-defective middle T mutants fail to induce mesoderm. These results suggest that early inductive signals and mitogenic and oncogenic stimuli may share common signal transduction pathways.

INTERCELLULAR SIGNALS ARE IMPORTANT in establishing the fundamental body plan and controlling the formation of organ systems during embryogenesis. These signals mediate early tissue-tissue interactions, called embryonic inductions, which have been well defined in amphibians by explantation and transplantation of embryonic tissues (*1, 2*). The earliest of these interactions is the induction of mesoderm by an interaction between presumptive endodermal and ectodermal tissues. Mesoderm normally forms from cells at the junction between the animal and vegetal hemispheres of the embryo (the marginal zone). Explanted cells from the animal hemisphere (animal caps) form only ectodermal tissue when cultured in isolation, but these same cells will form mesodermal tissue when placed in contact with vegetal (endodermal) cells (*1*). Several polypeptide growth factors or growth factor–like molecules [fibroblast growth factor (FGF), transforming growth factor–β2 (TGF-β2), and XTC mesoderm-inducing factor (MIF)] have been identified that can mimic the action of vegetal tissue in the induction of mesoderm in animal caps (*3–6*). Although the role of these growth factor–like molecules in the natural inductive process has not yet been directly demonstrated, maternal transcripts encoding FGF and a TGF-β homologous peptide (Vg1) have been identified in early embryos (*5, 7*). These observations suggest that membrane-associated signal transduction mechanisms associated with the mitogenic action of growth factors such as FGF may also be involved in early embryonic induction.

Although pharmacological agents are available for the investigation of a few signal transduction pathways in *Xenopus* embryos, for example, 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) as an exogenous activator of protein kinase C (*8*), microinjection of

Table 1. Induction of mesoderm by middle T mRNA injection. Summary of mesoderm induction in isolated animal caps by microinjected middle T mRNA as distinguished by morphological elongation and histological identification of muscle and notochord.

Affected area	Control (H_2O)	Mutant middle T (NG59)	Wild-type middle T
Elongation/constriction	3/144 (2%)	11/152 (7%)	57/142 (40%)
Notochord	0/25 (0%)	0/35 (0%)	10/62 (16%)
Muscle	0/30% (0%)	0/39% (0%)	17/55 (31%)

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mRNAs that encode regulatory proteins may provide a more specific and generally useful approach to the study of putative signaling mechanisms in early induction. By specifically activating or inhibiting potential regulatory proteins, it should be possible to assess whether the induction of mesoderm occurs through signaling pathways similar to those proposed to mediate growth factor–stimulated mitogenesis in cultured fibroblasts. These potential signaling pathways include the activation of both tyrosine and serine protein kinases (*9*), membrane phospholipid metabolism, and nuclear proto-oncogene transcription (*10*). We have used the viral oncogene polyoma middle T as a probe to investigate whether manipulation of intracellular signals can trigger mesodermal induction.

Polyoma middle T is localized to the plasma membrane and associates with and activates the cellular tyrosine kinase $pp60^{c\text{-}src}$ (*11–13*); it also forms a complex with an additional cellular tyrosine kinase, $pp62^{c\text{-}yes}$ (*13*) and a cellular phosphatidylinositol (3) kinase [(PI(3) kinase] (*14, 15*). Nontransforming mutants of middle T are partially or completely defective in their association with these cellular enzymes, indicating that these associations may be necessary for the oncogenicity of polyoma middle T. However, this does not rule out the possibility that other as yet uncharacterized cellular targets may be important in middle T function (*13*). To test the ability of middle T to trigger mesodermal induction, we synthesized mRNA encoding wild-type middle T or a nontransforming middle T mutant (NG59) in vitro and microinjected it into fertilized eggs at first cleavage. Injected embryos were allowed to develop to the early blastula stage (500 to 2000 cells) and animal caps were dissected and cultured in isolation for 48 hours. The induction of mesoderm in these animals caps was assessed by several criteria, including morphogenetic elongation and the formation of the characteristic mesodermal derivatives notochord and muscle.

Animal caps exposed to inducing polypeptides such as MIF, FGF, and TGF-β2 undergo an elongation believed to reflect the cellular movements of convergent extension associated with gastrulation in the intact embryo (*16*). Animal caps from embryos injected with wild-type middle T, but not those injected with the transformation-defective mutant NG59, become distended and elongated in a manner similar to caps treated with FGF or TGF-β2 (Fig. 1). When dissected animal caps were fixed, sectioned, and stained, those from embryos injected with wild-type middle T mRNA showed development of considerable internal structure, including notochord and muscle (Fig. 1). Sections of caps from embryos injected with mutant (NG59) middle T mRNA or water gave rise only to "atypical epidermis," although NG59 middle T–injected caps occasionally gave rise to large internal vacuoles. Neither wild-type nor NG59 middle T significantly affected the rate of division or final number of blastomeres at the time of dissection. A decrease in the division rate of blastomeres near the site of injection of wild-type middle T mRNA is occasionally observed.

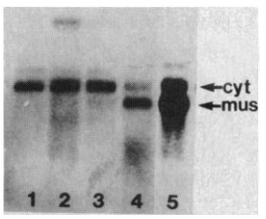

Fig. 2. Muscle actin mRNA induction in animal caps. Total RNA was extracted from animal caps prepared from embryos injected with synthetic mRNAs as described below. Total animal cap (four caps per lane) or intact embryo (one embryo per lane) RNA was extracted 40 hours after fertilization for a Northern blot and probed with a muscle actin–antisense RNA transcript. Muscle actin is indicated with an arrow (mus), and the higher band corresponds to cytoskeletal actin (cyt). Lane 1, H_2O-injected; lane 2, mutant middle T NG59–injected; lane 3, mutant middle T DL23–injected; lane 4, wild-type middle T–injected; lane 5, intact neurula (stage 22) embryo.

The histological identification of blocks of muscle caps from middle T–injected embryos was confirmed by immunohistochemistry with a muscle-specific antibody (Ab 12101) (*17*). Blocks of muscle were observed in animal caps from embryos injected with wild-type middle T mRNA, but not in caps from embryos injected with NG59 middle T mRNA or water. Muscle was always observed to arise in single large blocks rather than multiple patches, suggesting either a localized cooperative effect in the differentiation of muscle tissue or differential migration and adhesion of presumptive muscle cells.

During normal embryogenesis, muscle actin RNA is transcribed specifically in the somites and is often used as an early molecular marker for mesodermal induction (*2*). The injection of wild-type middle T mRNAs induced muscle actin transcripts, whereas NG59 and another nontransforming middle T mutant, DL23, did not, even at high injection doses (20 ng per embryo) (Fig. 2). We have also found that as little as 2 to 5 ng of middle T mRNA can induce detectable mesoderm. Induction of muscle mRNA by wild-type middle T was, however, weaker than is observed in untreated whole embryos of a comparable stage. This is true even when middle T mRNA was injected at the maximal nontoxic dose (25 ng per embryo).

The data on induction of mesoderm by middle T mRNA injection is summarized in

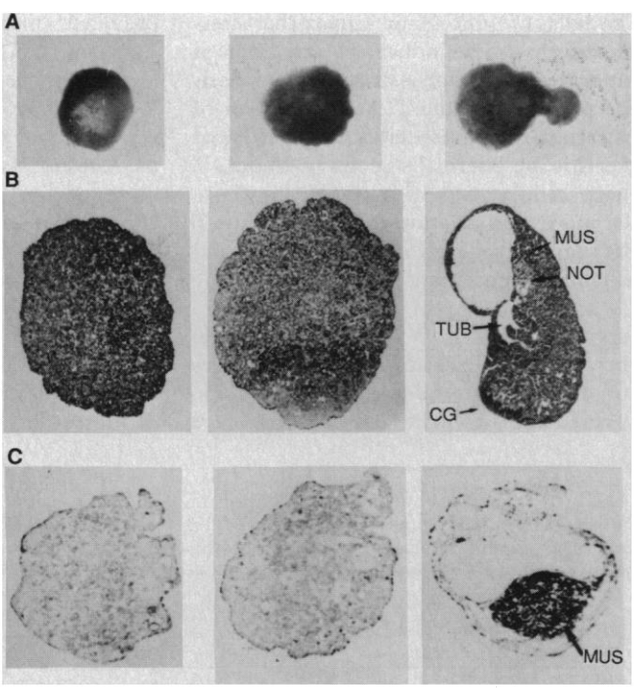

Fig. 1. Mesoderm formation in middle T–injected *Xenopus* embryos. (**A**) Elongation of animal caps. Animal caps were dissected at blastula stage (stage 7.5 to 8) from embryos injected at first cleavage in the animal-equatorial region of the egg with water (left panel), 10 to 20 ng of mRNA encoding NG59 middle T (middle panel), or wild-type middle T (right panel). (**B**) Giemsa-stained histological sections of animal caps from embryos injected with water (left panel), NG59 middle T RNA (center panel), or wild-type middle T RNA (right panel). Arrows indicate muscle (MUS), notochord (NOT), cement gland (CG), and a differentiated tubular structure that may be neural or pronephric (TUB). (**C**) Immunohistochemical identification of muscle in animal caps sections. Sections of caps prepared from embryos injected with water (left panel), NG59 middle T (middle panel), or wild-type middle T (right panel) were stained with a muscle antigen specific antibody (12101) and alkaline phosphatase–coupled second antibody. Arrow indicates large block of muscle (mus).

Table 1. Approximately 40% of animal caps from wild-type middle T mRNA–injected embryos showed significant elongation; 16% showed detectable notochord and 31% showed blocks of muscle tissue. Although animal caps injected with NG59 middle T mRNA showed more elongation than water-injected controls, neither muscle nor notochord were detected in caps from NG59 mRNA–injected embryos. In no RNA injection experiment did induction of detectable mesodermal structures exceed 70%. This is in marked contrast to treatment of animal caps with saturating doses of FGF or MIF proteins, which reproducibly produce mesodermal tissue in 90 to 100% of induced caps (*3, 4*). It is possible that this reflects a limitation of the mRNA microinjection procedure; microinjection of total polyadenylated mRNAs from *Xenopus* ovaries or XTC tissue culture cells also induces mesoderm with an efficiency between 50 and 75% (*18*). In separate experiments with ^{35}S-labeled RNA, we have observed that mRNA injected at the one-cell stage is distributed to all daughter blastomeres at the 32- to 256-cell stage (*19*).

Middle T–associated kinase activity was detectable in immunoprecipates from both elongated and nonelongated animal caps, but two- to threefold more activity was present in elongated caps than in nonelongated caps (*20*). It is therefore possible that in some caps the level of active middle T protein fails to achieve a threshold necessary for induction.

The use of a viral oncogene to study intracellular signaling in mesodermal induction is predicated on the assumption that this oncogene activates the same signaling pathways in *Xenopus* blastomeres that are activated during transformation of murine fibroblasts. The inability of nontransforming mutants of middle T to induce mesoderm indicates that similar biochemical functions are required for the transforming and the mesoderm-inducing functions of middle T. As discussed above, middle T is believed to transform fibroblasts at least in part via its interaction with pp60$^{c\text{-}src}$ and PI(3) kinase. We therefore investigated whether middle T associates with these same putative mediators in *Xenopus* blastomeres (Fig. 3).

Middle T–associated tyrosine kinase activity can be conveniently assayed in antibody to T immunoprecipitates with middle T itself as a substrate (*21*). Middle T mRNA was injected into fertilized eggs as described above, and embryos were allowed to develop to the blastula stage. The embryos were then lysed, and middle T was immunoprecipitated with an anti-T polyclonal antibody. This immunoprecipitate was incubated for 10 min with 1 μM ^{32}P-labeled adenosine triphosphate (ATP) and 10 mM $MnCl_2$, and the products were analyzed by SDS–gel electrophoresis. A major 56- to 58-kD protein that comigrated with middle T was observed to be phosphorylated in immunoprecipitates from wild-type middle T–injected embryos, but not NG59 middle T–injected embryos. No incorporation of phosphate into this band was observed when preimmune serum was used instead of anti-T antibody. More than 80% of the phosphate incorporated into wild-type middle T was found to be phosphotyrosine upon phosphoamino acid analysis (*20*). Middle T–associated tyrosine kinase activity was also immunoprecipitated from dissected animal caps and was detectable 24 hours after mRNA injection (*20*).

When parallel immunoprecipitates were assayed in the presence of phosphatidylinositol (PI) (200 μg/ml) and ^{32}P-labeled ATP 10 μM and the reaction products were extracted and analyzed by thin-layer chromatography (TLC) (*14, 15*), ^{32}P-labeled product comigrating with phosphatidylinositol (3)phosphate [PI(3)P] was observed in anti-T immunoprecipitates from embryos injected with wild-type middle T. No PI(3)P was observed in immunoprecipitates made with preimmune serum or from NG59-injected embryos. Taken together the results indicate that wild-type middle T, but not a nontransforming middle T mutant, associates with the same cellular effectors in early *Xenopus* embryos as have been proposed as critical elements of its mitogenic and oncogenic functions (Fig. 3). Microinjection of mRNA encoding a constitutively activated chicken pp60$^{c\text{-}src}$ mutant (*22*) does not appear to be sufficient to induce mesoderm (*20*), suggesting that activation of other cellular effectors may be necessary for mesodermal induction.

The proposal that a fibroblast mitogen, FGF, may constitute at least one component of the natural mesodermal inductive signal has raised the question of whether intracellular signal transduction pathways associated with mitogenesis are involved in the mediation of embryonic inductive signals (*4, 5*). Our data support this idea and demonstrate that microinjection of cloned mRNAs for regulators of putative signaling pathways may be a useful tool in addressing this question. Several oncogenes have previously been demonstrated to cause the appearance of differentiated characteristics on introduction into transformed cell lines (*23*) but our data indicate that an oncogene can shift embryonic cells from one developmental pathway (ectoderm) to another (mesoderm). Whether the specification of cell fates in early development is a normal function of cellular oncogenes requires further study.

These observations raise a number of

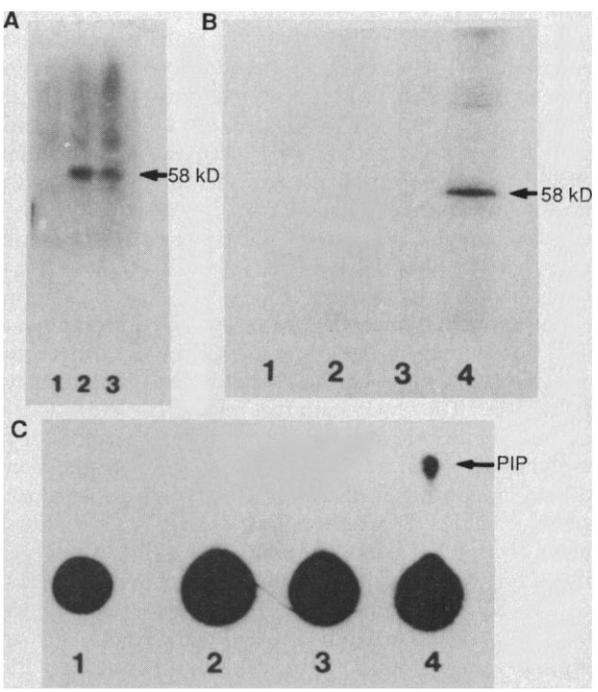

Fig. 3. Protein and PI kinase activities in middle T immunoprecipitates. Embryos were injected with middle T mRNA at first cleavage and grown to stage 7, lysed, and immunoprecipitated with anti-T antibody in acknowledgements. For determination of embryonic protein immunoprecipitation, mRNA-injected embryos were reinjected with 0.5 mCi of ^{35}S-labeled methionine at morula stage 3 to 4 and allowed to incorporate label until blastula stage 7. Immunoprecipitates were then assayed in vitro for protein or PI kinase activities as previously described (*14, 21*). (**A**) Protein immunoprecipitation from injected embryos. Immunoprecipitations were prepared with an anti-T polyclonal antibody from embryos labeled with [^{35}S]methionine and injected with H_2O (lane 1), NG59 middle T mRNA (lane 2), or wild-type middle T (lane 3). (**B** and **C**) Immunoprecipitates prepared with nonimmune (lane 1) or anti-T sera from embryos injected with H_2O (lane 2), NG59 mT RNA (lane 3), or wild-type middle T (lanes 1 and 4) were assayed for protein kinase (B) or PI(3) kinase (C) activities. Arrow in (B) indicates phosphorylated middle T, a 58-kD protein; arrow in (C) indicates phosphatidylinositol phosphate (PIP).

questions. The first is whether there are multiple components to the mesodermal inductive signal. Slack *et al.* (*4*) found that bovine FGF induces predominantly ventrolateral mesodermal tissues such as blood, mesenchyme, and muscle, but only very rarely induces notochord, the most characteristic dorsal mesodermal structure. In contrast, Smith (*3*) found that the *Xenopus* MIF commonly induces both muscle and notochord. We observed induction of muscle and, at lower frequency, notochord by middle T. Whether these differences simply reflect the relative strengths of the inducing signals generated by FGF, MIF, and middle T or the generation of a distinct "dorsalizing" signal remains to be determined.

A second question is whether activation of any of a number of distinct mitogenic and oncogenic signaling pathways is sufficient to induce mesoderm. Although Slack *et al.* (*4*) found that FGF and embryonal carcinoma-derived growth factor (ECDGF) were the only peptide mitogen among many tested to induce mesoderm, it is not known whether this specificity is determined by receptor expression or the activation of an FGF-specific intracellular signaling pathway. Although there is evidence that the fibroblast mitogen platelet-derived growth factor (PDGF) may activate similar signaling pathways to those activated by middle T (*21, 24*), there is no direct evidence that FGF shares these same signaling pathways. FGF does, however, appear to elevate cellular diacylglycerol (*25*) and to increase cellular tyrosine phosphorylation (*26*), suggesting that FGF- and middle T–activated signal transduction pathways may overlap. Introduction of other oncogenes (for example, p21ras) or growth factor receptors (for example, PDGF receptor) may clarify whether the mesodermal differentiative program is activated by a single, specific intracellular signal or by any of a number of mitogen-stimulated mediators.

The third question is whether the intracellular signaling pathway (or pathways) is actually activated during the natural inductive process. The observation that middle T can activate mesodermal differentiation does not in itself demonstrate that natural mesodermal induction is mediated by any of the known middle T targets (for example, $pp60^{c\text{-}src}$, $pp62^{c\text{-}yes}$, and PI(3) kinase). Furthermore, it does not address the question of how many different types of endogenous or artificial signals may be capable of inducing mesoderm. It does, however, indicate cellular regulatory proteins that may be investigated as potential mediators of natural inductive signals. Further work to clarify the number and specificity of possible intracellular messengers of mesodermal induction is necessary; the microinjection of mRNAs encoding putative regulators should prove useful in addressing these points.

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Global Sea Level Rise and the Greenhouse Effect: Might They Be Connected?

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Secular sea level trends extracted from tide gauge records of appropriately long duration demonstrate that global sea level may be rising at a rate in excess of 1 millimeter per year. However, because global coverage of the oceans by the tide gauge network is highly nonuniform and the tide gauge data reveal considerable spatial variability, there has been a well-founded reluctance to interpret the observed secular sea level rise as representing a signal of global scale that might be related to the greenhouse effect. When the tide gauge data are filtered so as to remove the contribution of ongoing glacial isostatic adjustment to the local sea level trend at each location, then the individual tide gauge records reveal sharply reduced geographic scatter and suggest that there is a globally coherent signal of strength 2.4 ± 0.90 millimeters per year that is active in the system. This signal could constitute an indication of global climate warming.

DURING THE PAST CENTURY, SEA level, as recorded on tide gauges situated at stations around the world, has apparently risen by 10 to 20 cm, no more than 25% of which may apparently be attributed to the steric effect of thermal expansion of the oceans (*1–3*). The dominant cause of rising sea levels must therefore be the increase of the mass of water in the global oceans, most probably due to melting of land-based ice sheets and glaciers (*4*). Because general circulation model simulations have shown that the climatic warming expected from increasing atmospheric loads of CO_2 and other greenhouse gases is strongly focused in polar latitudes [for example (*5*)], observations of rising sea level have been construed as a first indication of this climatic change (*1, 2*).

A serious impediment to acceptance of this interpretation has been that the observed rates of sea level rise exhibit such large geographic variability (the standard deviation is as large as the mean) as to seriously question the hypothesis that they reveal any globally coherent signal. The problem is especially acute because the coverage of the southern oceans with gauges of sufficient seniority is poor. In this report we demonstrate that when the tide gauge data are corrected for contamination due to the ongoing influence of glacial isostatic adjustment, the global pattern thereby revealed does have high spatial coherence.

The process of glacial isostatic adjustment continues to substantially influence the record of relative sea level (RSL) change, even though the last major deglaciation event was complete more than 6000 years ago, because

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