

# The specific induction of *myc* proto-oncogene expression in normal human B cells is not a sufficient event for acquisition of competence to proliferate

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It is known that competence to proliferate is a function of the B cell. The B cell is a terminally differentiated cell that is capable of proliferating in response to antigenic stimulation. The B cell is a terminally differentiated cell that is capable of proliferating in response to antigenic stimulation.

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**ABSTRACT** Resting human B cells can be activated to proliferate in the presence of both polyclonal antibodies to immunoglobulin  $\mu$ -heavy chain and B-cell growth factor (BGF). This process appears to be temporally controlled in that the initial activation of the B cells and their responsiveness to BGF is determined by polyclonal anti- $\mu$  chain antibodies alone. We have used this system to investigate the role of the *myc* gene in the B cell cycle of normal human peripheral blood cells. Our results show that the polyclonal anti- $\mu$  chain antibodies induced B cell activation is accompanied by a specific induction of *myc* gene expression without proliferation, subsequent entry into the S phase of the cell cycle. BGF is added. Monoclonal antibodies to either  $\mu$  chain of the pan B cell antigen IgM also reveal a similar *myc* gene transition and activation of *myc* gene expression. However, unlike activation with polyclonal anti- $\mu$  chain antibodies, cells stimulated with these monoclonal antibodies do not acquire responsiveness to BGF. The results imply that additional stimulatory functions must be present to potentiate the specific function induced by the B cells to acquire the capacity to proliferate in response to BGF. These findings are discussed in relation to the origin of B cell malignancies.

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Several lines of experimental evidence suggest that the *myc* proto-oncogene functions as a key correlate in the induction pathway to competence for cell proliferation (1,2). In mouse B and T cells, Kelly et al. demonstrated that *myc* gene expression could be induced by antigens prior to DNA synthesis (3). More recently, a *myc* gene expression in quiescent mouse T lymphocytes by PMA (4) and by other stimuli (5) has been reported. In the B cell system, the *myc* gene is induced by polyclonal anti- $\mu$  chain antibodies (6) and by monoclonal anti- $\mu$  chain antibodies (7). In the T cell system, the *myc* gene is induced by PMA (4) and by other stimuli (5).

In the B cell system, the *myc* gene is induced by polyclonal anti- $\mu$  chain antibodies (6) and by monoclonal anti- $\mu$  chain antibodies (7). In the T cell system, the *myc* gene is induced by PMA (4) and by other stimuli (5).

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one function of the *myc* protein product may be to promote an acquisition of competence to respond to exogenously added growth factors.

To further study the influence of transcriptionally activated *myc* gene upon normal human phenotypes, we utilized the *myc* gene pathway of human B cells, purified from peripheral blood, as a model system of choice. Under certain conditions, the stimulation of B cells to acquire competence to proliferate can be divided into at least two distinct steps. First, B cells can be activated initially by antigenic stimulation with T cells or by cross-linking of surface immunoglobulin (Ig) by antigen or anti- $\mu$  (8,9). This treatment renders the cells responsive to a second well-defined "growth factor," factors such as the B-cell growth factor (BGF), and this step is even possibly producing the acquired responses for these factors (10-12). As noted in the report, the experimental description of the activation and differentiation of B cells is not yet fully directed, further the *myc* gene expression is not yet fully directed. Thus, this system provides us with the means to penetrate the link between *myc* expression and cell proliferation.

## MATERIALS AND METHODS

**B Cell Purification.** Human B cells were purified from human peripheral blood mononuclear cells (PBMC) by a series of steps. First, PBMC were treated with a cocktail of antibodies to T cells and monocytes, and the B cells were purified by a series of steps.

**Antibody Stimulation.** B cells were stimulated by a series of steps. First, B cells were treated with a cocktail of antibodies to T cells and monocytes, and the B cells were purified by a series of steps.

**B Cell Activation.** B cells were activated by a series of steps. First, B cells were treated with a cocktail of antibodies to T cells and monocytes, and the B cells were purified by a series of steps.

**Antibody Stimulation.** B cells were stimulated by a series of steps. First, B cells were treated with a cocktail of antibodies to T cells and monocytes, and the B cells were purified by a series of steps.

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