1. State of the Problem

The well-characterized basic functions of the Na+/K+ pump include: (1) maintenance of the transmembrane Na+ and K+ gradients over the plasma membrane, which is a prerequisite for the generation of the resting membrane potential and the action potential; (2) generation of the transmembrane electrochemical potential gradient for Na+ ions which provides the energy for the uphill movements of \( \text{H}^+ \) and \( \text{Ca}^{2+} \) ions as well as sugars and amino acids through the appropriately coupled transfer devices; (3) maintenance of the high [K+] environment which is required for the optimum activity of many intracellular enzymes involved in energy generation and macromolecule synthesis. In the outcome, the Na+/K+ pump plays a key role in the regulation of normal cellular homeostasis, cell differentiation and cell proliferation.

The enzymatic machinery in the Na+/K+ pump is the Na+/K+-transporting ATPase EC 3.6.1.37 (Na/K-ATPase) which uses the energy from the hydrolysis of terminal phosphoryl of one molecule of intracellular ATP to transport across the cell membrane three Na+ ions outwards and two K+ ions inwards against steep electrochemical gradients. So, ATP, intracellular Na+ ions and extracellular K+ ions may be viewed as substrates, and ADP, orthophosphate, extracellular Na+ ions and intracellular K+ ions as products of the enzymatic process.

The role of the Na+/K+ pump in normal and cancer cell proliferation is less well defined as emerges from the perusal of recent monographs (Boynton et al. 1982, Galeotti et al. 1982, Padilla and McCarty 1982, Glynn and Ellory 1985) and reviews (J.G. Kaplan 1978, Glynn 1985). In the control of cell proliferation direct

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correlations and requirements for changes in ion fluxes, ion content and Na\textsuperscript{+}/K\textsuperscript{+}-ATPase activity have been documented, but disappointingly no explicit cause and effect relationships have evolved, and no actual mechanisms by which changes in [Na\textsuperscript{+}], [K\textsuperscript{+}] and Na/K-ATPase activity exert a regulatory function have been discovered to date as stated by Sparks et al. (1982).

The present chapter is the first endeavour to develop a coherent picture of the role of the Na\textsuperscript{+}/K\textsuperscript{+} pump in cell proliferation that is consistent with all well-established data. More specifically, it offers answers to two major questions that have remained as yet largely unresolved (de Laat and van der Saag 1982), namely: (1) how does the cell control Na\textsuperscript{+}/K\textsuperscript{+} pumping? (see Sect. 3), and (2) through which pathways do the transport changes exert their influence on cell cycle-dependent metabolic and synthetic processes? (see Sect. 5). This chapter concludes with an assessment of the suitability of the Na\textsuperscript{+}/K\textsuperscript{+} pump as a target for detecting and developing tumour inhibitors of novel, specific mechanisms of action (see Sect. 6).

2. Coupling of Na\textsuperscript{+}/K\textsuperscript{+} Pump Power Switch-Up to Cell Proliferation

Proliferation of normal and cancer cells is indispensably coupled with switch-up of the Na\textsuperscript{+}/K\textsuperscript{+} pump power of a cell (for representative reviews see J.G. Kaplan 1978, Rozengurt and Mendoza 1980, Leffert 1982, Rozengurt 1982, Mendoza et al. 1986). The available comprehensive evidence may be summarized in the following statements.

(1) All kinds of growth promoters (e.g. fetal calf serum and the various specific growth factors or mitogens) enhance the Na\textsuperscript{+}/K\textsuperscript{+} pump power of quiescent cells of all types. The large rise of pump power per cell is one of the earliest events in cell proliferation. (2) Prevention of Na\textsuperscript{+}/K\textsuperscript{+} pump power switch-up by any means whatever blocks cell proliferation. The initial event, providing pumping enhancement, is the growth promoter-elicited Na\textsuperscript{+} influx into the cell through the Na\textsuperscript{+}/H\textsuperscript{+} exchanger. So, removal of extracellular Na\textsuperscript{+} or intervention of amiloride (cf. L’Allemain et al. 1984a), which both eliminate the Na\textsuperscript{+} influx, suppress initiation of DNA synthesis and cell proliferation. The same follows from the blockade of pump power switch-up by removal of extracellular K\textsuperscript{+}, needed for coupled Na\textsuperscript{+}/K\textsuperscript{+} antiport, or by application of cardiac glycosides like ouabain, established as specific pump inhibitors. (3) The ouabain concentration required for the suppression of proliferation of a given cell line is the same for all types of growth promoters indicating that the Na/K-ATPase is generally the target of this proliferation inhibitor. The sensitivity or resistance of the pump to inhibition by various cardiac glycosides correlates with the susceptibility or resistance of a cell line to inhibition of growth by the various glycosides (Mayhew 1972, Saishu et al. 1985). The dose response of ouabain-produced inhibition of Na\textsuperscript{+}/K\textsuperscript{+} pumping and cell proliferation is closely correlated (Segel and Lichtman 1980). (4) The increase of Na\textsuperscript{+}/K\textsuperscript{+} pumping at the G\textsubscript{i}/S transition during the cell cycle is a prerequisite for entry into the S-phase; the complete inhibition of pumping by