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Quantum chemistry PM3 calculations of sixteen mEGF molecules

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Abstract. Murine epidermal growth factor (mEGF) is a single polypeptide of fifty-three amino acid residues containing three intramolecular disulfide bonds, widely found in body fluids like milk. We performed semi-empirical quantum chemistry calculations on sixteen mEGF molecules at level of PM3 to investigate the electronic properties of these molecules. The equilibrium structure, heats of formation, molecular orbitals, polarizability, and dipole moment were computed in vacuum and in solvents (carbon tetrachloride, ethanol, and water). Electronic structure calculations in vacuum show that the highest occupied molecular orbital (HOMO) of all mEGF molecules distributes on five C-terminal residues (Tyr49/Tyr50 and Arg48/Arg53 residues), while the lowest unoccupied molecular orbital (LUMO) locates on the disulfide bonds, indicating that the disulfide bridges and C-terminus are important for the biological activity of EGF. The locations of LUMO and HOMO show almost no solvent effects. In the solvent of relative larger dielectric constant, the heat of formation and mean polarizability of the mEGF molecules become lower while the dipole moment is enhanced. Examination of the locations of hydrogen bonds demonstrates that the B loop (residues 14-31) is crucial for the conformational stability and biological activity of EGF. All these theoretical results are in general agreement with experiments. We suspect that the N- and C-terminal residues play some roles in stabilizing the molecular conformation of EGF, probably associated with the orientation of EGF binding to EGFR (epidermal growth factor receptor).

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1 Introduction

EGF (53 amino acid residues) was discovered by Stanley Cohen in 1962 who won the Nobel Prize in 1986. EGF is a kind of micro-molecule polypeptide widely found in human and other animals in vivo. Human EGF gene is located on chromosome 4 [1]. The presently known experimental structures of murine EGF (mEGF) have essentially the same folding as human EGF [2,3]. EGF adopts a well-defined 3D structure and comprises three distinct loops (as shown in Fig. 1) determined by three disulfide bridges [2–5]; these disulfide bridges are essential for structural stability and biological activity. The conformation of EGF, like many other small disulfide proteins, is determined essentially by its amino acid sequence alone [6,7].

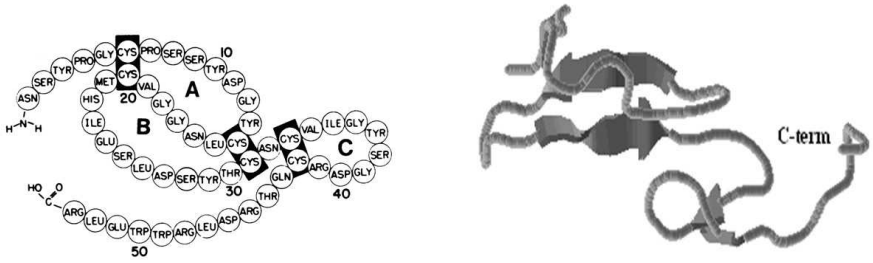

Figure 1: Molecular structure of mEGF: (a) proximity relation of residues in folding peptide skeleton, the black bands denote the disulfide bonds [30]; (b) cartoon rendering for NO.5 mEGF molecule.

EGF regulates cell proliferation and differentiation by binding to its receptor (EGFR) extra-cellular domains [4,6,8,9]. The EGF receptor is a transmembrane protein tyrosine kinase. Binding of EGF to the extracellular region of EGFR induces receptor dimerization [10–12], which is supposed to bring the two cytoplasmic tyrosine kinase domains of the receptors close enough for autophosphorylation and thereby to activate the intrinsic tyrosine kinase activity [13–17]. The EGF receptor tyrosine kinase triggers numerous downstream signaling pathways. Thus, EGF plays an important role in embryonal development, tissue repair, wound healing [18], carcinogenesis, blood coagulation, fibrinolysis, neural development, and cell adhesion [19–21]. Besides, EGF is mitogenic for a number of cell types and demonstrates a variety of actions in vitro and in vivo, including stimulation of metabolite transport, activation of glycolysis, stimulation of production of RNA, protein, and DNA, enhancement of cell proliferation, alteration of cell morphology, and inhibition of gastric acid secretion [6,8,19,21–23].

Due to its biological effect, EGF has many potential applications in clinical medicine and cosmetics. A variety of N-/C-terminus truncated and residues mutated forms have been used in experiments to locate the biologically active sites of EGF molecules and to investigate their functions. However, there have been some debates on the function of C-terminal residues. Deletion of the C-terminal five or six residues results in a marked reduction in both receptor affinity and mitogenic activity in vitro [3,18,24–26]. On the