

IMMUNOHISTOCHEMICAL LOCALIZATION OF THE EGF-RECEPTOR IN HUMAN TISSUES USING A HUMANIZED MONOCLONAL ANTIBODY.

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The epidermal growth factor receptor (EGFR) and its ligands, epidermal growth factor (EGF) and transforming growth factor alpha (TGF-alpha), are widely distributed in the human tissues and are thought to play an important role during development, regeneration, differentiation and transformation of the cells from different tissues [1]. EGFR is overexpressed by several human tumors and scantily detectable in most normal tissues [2]. The introduction of Monoclonal Antibodies (Mab) and more recently engineered humanized Mabs have greatly expanded the therapeutic potential of this modality of cancer treatment. The h-R3 Mab is a IgG1 humanized antibody that was obtained by cloning the variable region of the murine egf/r3 Mab, which exhibited a similar ability to inhibit the EGF-binding to its receptor as compared with the original murine egf/r3 Mab [3]. This Mab has been used successfully in several phase I/II clinical trials in patients with advanced tumor of epithelial origin over expressing EGFR [4].

Biotinylated h-R3 Mab was tested in both fetal and adult normal tissues as well as in fresh tumor samples by ABC peroxidase technique. All fetal tissues studied including skin, stomach, small and large Intestine (Figure 1 A), cerebellum, brain, adrenal gland, liver, spleen, kidney (Figure 1 B), pancreas, heart and prostate (Figure 1 C) were positive for h-R3 Mab, showing two different staining patterns, one homogeneous and finely granular in cytoplasm and another grosser with intense labeling in both membrane and cytoplasm. The humanized antibody has a similar recognition pattern to that of the parenteral murine Mab in adult normal tissues. An intense reactivity was evidenced in skin (Figure 1 D), tongue, gastrointestinal tract (Figure 1 E), renal tubules (Figure 1 F) and breast epithelium. Tissues from the central nervous system and the genitourinary system showed faint staining, whereas those from cardiovascular and lymphoid tissues proved to be negative. This antibody exhibited a heterogeneous and strong membrane and cytoplasm staining in 50% of both, the lung (5/10) and (8/16) breast cancer tumors (Figure 1 G). All head and neck squamous cell carcinomas studied were also positive (Figure 1 H and I).

EGFR has been found mainly in the cellular membrane and the basolateral region of the epithelial cells and the number of receptors is greater in proliferating cells, neoplastic cells and carcinoma cell lines [5]. The data presented reveals the ubiquitous distribution of the receptor in the developing mucosa of gut segments as well as in the various epithelial cell types. EGFR expression was more restricted in the corresponding adult tissues and highly expressed in the studied epithelial cancer tissues using h-R3. The widespread distribution of EGFR suggests that it has many functions during mammalian development, organ repair in adults, as well as in malignant transformation. These data and the clinical results with h-R3 suggest that this Mab should be taken into account

when evaluating antitumoral drugs to target this receptor in the treatment of some epithelial malignancies.

References

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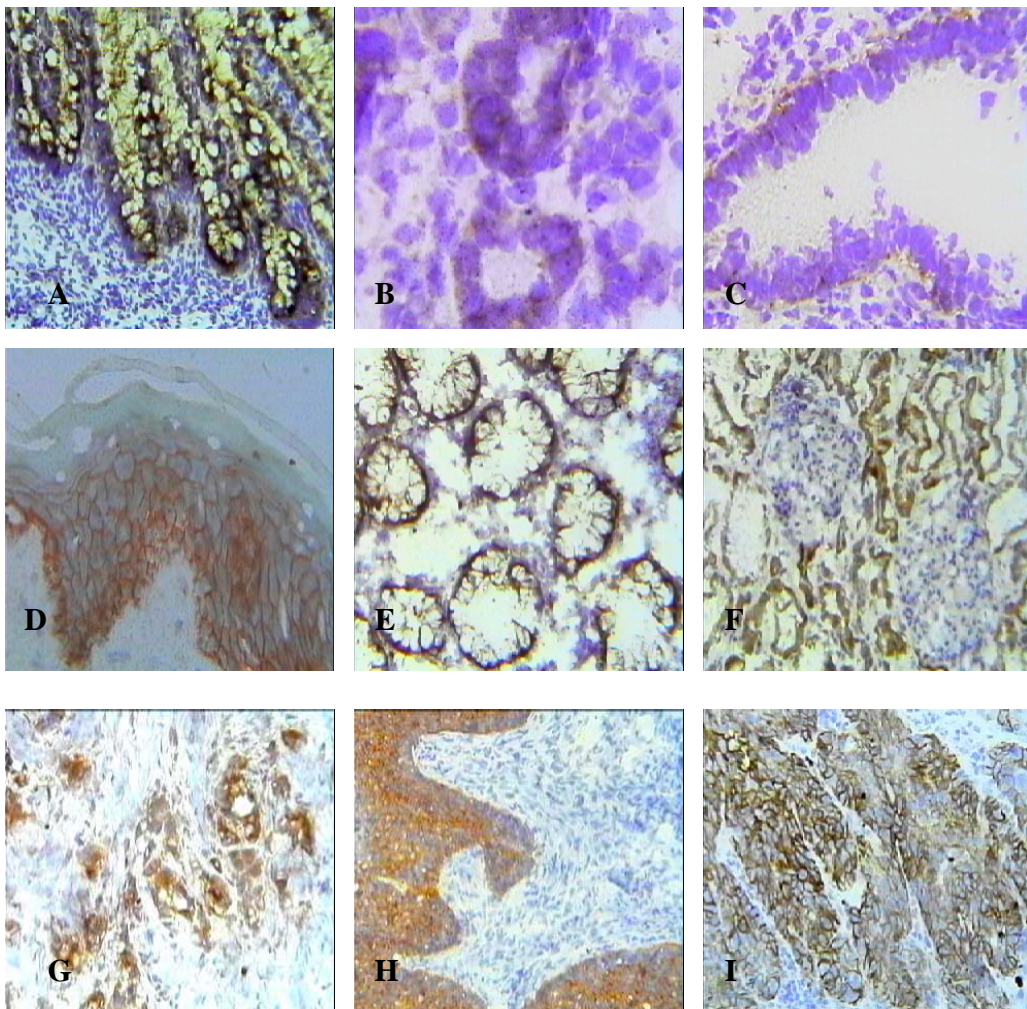


Figure 1. Staining pattern of h-R3 Mab in fetal (A-C), adult normal (D-F) and malignant tumors (G-I) tissues using ABC/HRP methods. Original magnification: A, E-I (100x); C-D (250X) and B (400X).