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Development of a Human Skin Explant Model for Drug Metabolism and Toxicity Studies

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Abstract : Skin toxicity is poorly detected during preclinical studies, and drug-induced side effects in humans such as rashes, hyperplasia or more serious events like bullous pemphigus or toxic epidermal necrolysis represent an important hurdle for clinical development. In vitro keratinocyte-based epidermal skin models are suitable for the detection of chemical-induced irritancy, but do not recapitulate the biological complexity of full skin and fail to detect potential serious side-effects. Normal healthy skin explants may represent a valuable complementary tool, having the advantage of retaining the full skin architecture and the resident immune cell diversity. This study investigated several conditions for the maintenance of good morphological structure after several days of culture and the retention of phase II metabolism for 24 hours in skin explants in vitro. Human skin samples were collected with informed consent from patients undergoing plastic surgery and immediately transferred and processed in our laboratory by removing the underlying dermal fat. Punch biopsies of 4 mm diameter were cultured in an air-liquid interface using transwell filters. Different cultural conditions such as the effect of calcium, temperature and cultivation media were tested for a period of 14 days and explants were histologically examined after Hematoxylin and Eosin staining. Our results demonstrated that the use of Williams E Medium at 32°C maintained the physiological integrity of the skin for approximately one week. Upon prolonged incubation, the upper layers of the epidermis become thickened and some dead cells are present. Interestingly, these effects were prevented by addition of EGFR inhibitors such as Afatinib or Erlotinib. Phase II metabolism of the skin such as glucuronidation (4-methyl umbeliferone), sulfation (minoxidil), N-acetyltransferase (p-toluidene), catechol methylation (2,3-dehydroxy naphthalene), and glutathione conjugation (chlorodinitro benzene) were analyzed by using LCMS. Our results demonstrated that the human skin explants possess metabolic activity for a period of at least 24 hours for all the substrates tested. A time course for glucuronidation with 4-methyl umbeliferone was performed and a linear correlation was obtained over a period of 24 hours. Longer-term culture studies will indicate the possible evolution of such metabolic activities. In summary, these results demonstrate that human skin explants maintain a normal structure for several days in vitro and are metabolically active for at least the first 24 hours. Hence, with further characterisation, this model may be suitable for the study of drug-induced toxicity.

Keywords : human skin explant, phase II metabolism, epidermal growth factor receptor, toxicity
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