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Research review paper

Biotechnological challenges of bioartificial kidney engineering

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ABSTRACT

With the world-wide increase of patients with renal failure, the development of functional renal replacement therapies have gained significant interest and novel technologies are rapidly evolving. Currently used renal replacement therapies insufficiently remove accumulating waste products, resulting in the uremic syndrome. A more preferred treatment option is kidney transplantation, but the shortage of donor organs and the increasing number of patients waiting for a transplant warrant the development of novel technologies. The bioartificial kidney (BAK) is such promising biotechnological approach to replace essential renal functions together with the active secretion of waste products. The development of the BAK requires a multidisciplinary approach and evolves at the intersection of regenerative medicine and renal replacement therapy. Here we provide a concise review embracing a compact historical overview of bioartificial kidney development and highlighting the current state-of-the-art, including implementation of living-membranes and the relevance of extracellular matrices. We focus further on the choice of relevant renal epithelial cell lines versus the use of stem cells and co-cultures that need to be implemented in a suitable device. Moreover, the future of the BAK in regenerative nephrology is discussed.

Contents

Abbreviations: AFDSc, amniotic fluid-derived stem cells; AKI, acute kidney injury; A2M, alpha-2-macroglobulin; AQP1, aquaporin 1; ARF, acute renal failure; BAK, bioartificial kidney; BCRP (*ABCG2*), breast cancer resistance protein; BM, basement membrane; BMP-7, bone morphogenetic protein 7; BMSCs, bone marrow-derived stem cells; BRECS, Bioartificial Renal Epithelial Cell System; CAM, cellular adhesion molecules; CD13, aminopeptidase-N; ciPTEC, conditionally immortalized proximal tubule epithelial cells; CKD, chronic kidney disease; ECM, extracellular matrix; EGF, epidermal growth factor; ESCs, embryonic stem cells; ESRD, end stage renal disease; FGF-2, fibroblast growth factor-2; FGFR-2, fibroblast growth factor receptor-2; GAGs, glycosaminoglycans; G-CSF, granulocyte colony-stimulating factor; GGT, γ-glutamyltransferase; GLUT5, glucose transport protein 5; HFM PAES, high flux membrane polyarylethersulfone; HGF, hepatocyte growth factor; HK-2, human kidney cell line-2; HPTC, human primary tubular cell cultures; HRGEC, human renal glomerular endothelial cells; hTERT, human telomerase reverse transcriptase; HUVEC, human umbilical vein endothelial cells; IGF-I, insulin-like growth factor-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; iPSC, induced pluripotent stem cells; L-DOPA, 3,4-dihydroxy-L-phenylalanine; MATEs (*SLC47A1/2*), multidrug and toxin extrusion proteins (*Solute carrier family member 47A1/2 gene*); MOF, multiorgan failure; MRP2/-4 (*ABCC2/-4*), multidrug resistance protein 2/-4 (*ATP Binding Cassette transporter C2/4 gene*); NBC1, Na^+/HCO_3^- cotransporter 1; OAT1/-3 (*SLC22A6/-A8*), organic anion transporter 1/-3 (*Solute carrier family member 22A6/8 gene*); OATP4C1 (*SLCO4C1*), organic anion transporting polypeptide 4C1 (*Solute carrier family 21 member O4C1 gene*); OCT1/-2 (*SLC22A1/-A2*), organic cation transporter 1/-2(*Solute carrier family member 22A1/2 gene*); PDGF-A, platelet-derived growth factor alpha chain; PES, polyethersulfone; PET, polyethylene terephthalate; P-gp, MDR1 (*ABCB1*), P-glycoprotein, multidrug resistance 1 protein (*ATP Binding Cassette transporter B1 gene*); PSF, polysulfone; PTEC, proximal tubule epithelial cells; PVP, polyvinylpyrrolidone; RAD, renal assist device; SGLT2, sodium/glucose cotransporter 2; SV40t, Simian virus 40 T antigen; TCP, tissue culture polystyrene; TEER, transepithelial electrical resistance; TGF-β1, transforming growth factor-beta 1; UGT, UDG-glucuronosyltransferases; Upy, ureido-pyrimidinone; US FDA, United States Food and Drug Administration; VEGF, vascular endothelial growth factor; ZO-1, Zonula occludens-1.

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Introduction

The need for novel renal replacement therapies

The kidneys play a crucial role in the health balance of organisms by the excretion of waste products, the reabsorption of essential compounds and its endocrine and metabolic activities (Deetjen, 1989; Deneke and Fanburg, 1989; Layton, 2012; Maack, 1975; Tannen and Sastrasinh, 1984). The complex organ contains functional components, the nephrons, consisting of numerous cell types to fulfill its vital tasks (Fig. 1). Onset of acute kidney injury (AKI) or chronic kidney disease (CKD), can be multifactorial and caused by eg. hypertension, aging, obesity, diabetes mellitus, auto-immune disease or drug-induced nephrotoxicity (Artz et al., 2004; Fox et al., 2012; Glaudemans et al., 2012; Hoorn et al., 2011; Vanholder and De Smet, 1999; Winearls and Glassock, 2011). In CKD the retention and accumulation of a variety of endogenous metabolites is a hallmark, associated with a broad range of pathologies constituting the uremic syndrome. Patients undergoing chronic hemodialysis (3–4 times weekly) or peritoneal dialysis have a markedly reduced survival attributable to cardiovascular disease, hypertension, bone disorders and reduced cognitive function. Progression of renal disease through fibrosis can eventually lead to anuria (Boron and Boulpaep, 2003; Liabeuf et al., 2013; Pletinck et al., 2013; Vanholder et al., 2001, 2008).

Current dialysis therapies only partly replace renal excretion, suggesting that the waste products (putative uremic toxins) are actively being secreted by the kidneys rather than filtered. Vanholder and colleagues pioneered in establishing the European Uremic Toxin Workgroup Database (EUTox; http://www.uremic-toxins.org), and defined a list of over 150 compounds divided in three classes: 1) small water-soluble compounds (<500 Da) that readily pass dialysis membranes, 2) middle molecules (>500 Da) for which filtration is limited due to size and charge, and 3) the protein-bound solutes which are a class of compounds difficult to clear by current dialysis modalities. The removal of the latter group depends on active tubular secretion shifting protein binding to the free fraction. For this, the renal proximal tubule cells of the kidneys are equipped with multiple transporters with overlapping substrate specificities that vigorously cooperate in basolateral uptake and luminal (urinary) excretion (Masereeuw et al., 2014). In addition to the limited clearance capacity of the current renal replacement therapies, the lack of metabolic and endocrine functions contributes further to disease progression, morbidity and mortality (Krieter et al., 2010). Best treatment option is organ transplantation but a major shortage of donor organs (in Europe and the United States, the waiting list for a new patient nowadays is 4 years; Kidney Link, 2014), as well as complications related to immunosuppressive therapy after transplantation warrant novel approaches such as BAK development (Artz et al., 2004; Gellermann et al., 2013; Hoorn et al., 2011).

Historical overview of the BAK

The BAK is a promising biotechnological approach to replace essential renal functions, including excretory, metabolic and endocrine

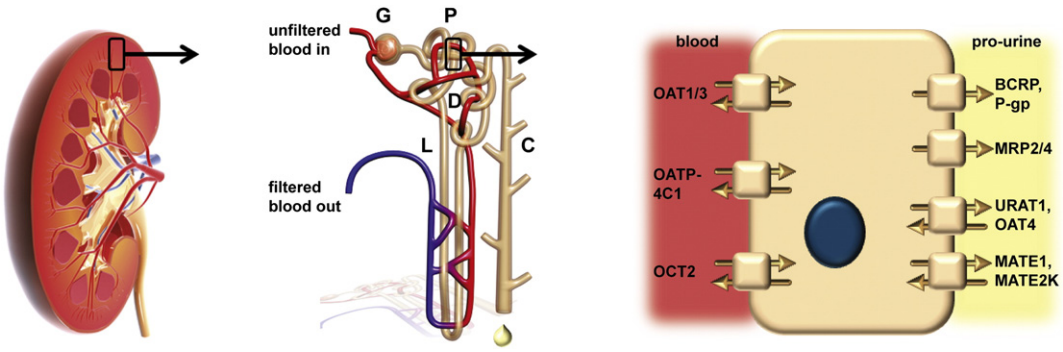

Fig. 1. Renal physiology from organ to cell. (left and middle) A cross-section of the human kidney which approximately consists of 1 million nephrons, the functional components of this organ. (Middle) Unfiltered blood will enter the glomerulus (G) and small solutes and H_2O will be excreted via ultrafiltration into Bowman's space which is contiguous with the lumen of the proximal tubule. Subsequently, the proximal tubule epithelial cells (P) will reabsorb H_2O and compounds such as amino acids, glucose and albumin from the filtered fraction, next to the active excretion of endo- and xenobiotics into the pro-urine mediated by in- and efflux transporters. In addition, 65% of the total amount of electrolytes will be reabsorbed via paracellular pathways. Downstream the proximal tubule segment the loop of Henle (L), the distal convoluted tubule (D) and collecting tubule and duct cells (C) are localized. In brief, these cell types are equipped with specific water and ion channels involved in the homeostasis of water and electrolyte balance, finally contributing to a healthy multi-organ microenvironment. (Right) Endogenous and exogenous solutes will be excreted into the lumen mediated via proximal tubule specific ATP-binding cassette — and solute carrier transporter proteins (e.g. basolateral influx organic anion transporter-1 and -3 (*SLC22A6*/OAT1, *SLC22A8*/OAT3), solute carrier organic anion transporter 4C1 (*SLCO4C1*/OATP4C1), organic cation transporter-2 (*SLC22A2*/OCT-2) and apical efflux breast cancer resistance protein (*ABCG2*/BCRP), P-glycoprotein (*ABCB1*/P-gp), multidrug resistance protein-2 and -4 (*ABCC2*/MRP2, *ABCC4*/MRP4), solute carrier 47A1 (*SLC47A1*/MATE1), solute carrier 47A2 (*SLC47A2*/MATE-2K), organic anion transporter-4 (*SLC22A9*/OAT4) and organic urate transporter-1 (*SLC22A12*/URAT1)).