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Animal Models in Burn Research

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Abstract

Burn injury is a severe form of trauma affecting more than two million people in North America each year. Burn trauma is not a single pathophysiological event but a devastating injury that causes structural and functional deficits in numerous organ systems. Due to its complexity and the involvement of multiple organs, *in vitro* experiments cannot capture this complexity nor address the pathophysiology. In the past two decades, a number of burn animal models have been developed to replicate the various aspects of burn injury; to elucidate the pathophysiology and explore potential treatment interventions. Understanding the advantages and limitations of these animal models is essential for the design and development of treatments that are clinically relevant to humans. This review paper aims to highlight the common animal models of burn injury in order to provide investigators with a better understanding of the benefits and limitations of these models for translational applications. While many animal models of burn exist, we limit our discussion to the skin healing of mouse, rat, and pig. Additionally, we briefly explain hypermetabolic characteristics of burn injury and the animal model utilized to study this phenomena. Finally, we discuss the economic costs associated with each of these models in order to guide decisions of choosing the appropriate animal model for burn research.

Introduction

Burn injury is among the most debilitating traumas to inflict humans. The incidence of burns in the United States is estimated to be more than two million cases per year [1], with 3400 deaths per year attributed to burn related injuries [2]. According to the World Health Organization [3], about 300,000 deaths worldwide each year are due to burns. Burn injury induces numerous organ dysfunctions resulting in high levels of morbidity and mortality [4], [5-7]. Particularly, burns of large surface area manifest into systemic problems like hypermetabolism [8-10] and sepsis [9,11]. The hypermetabolic cascade seems to involve two pathways in particular: glucose metabolism with insulin resistance (IR) and hyperglycemia [12,13],[14], and lipid metabolism with an increased lipolysis [15]. Moreover, sepsis is a heterogeneous syndrome defined by the systemic inflammatory response to infection [16]. The resources required to care for burn patients creates an enormous burden on the health care system. The annual cost of caring for burn patients in the United States is more than $573 million [1]. While over the last decade important

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advances have been made in reducing the mortality rate in burns [1], treatment is still far from ideal.

Animal models have greatly improved our understanding of the cause and progression of many human diseases and have proven to be a useful tool for discovering therapeutic drugs. For instance, mutant mice models have given us insights into the genetic pathways involved in diabetes [17] and obesity [18]. Additionally, the rat animal model has helped researchers identify the genetics behind cardiovascular diseases like hypertension and atherosclerosis [19]. Perhaps, the biggest contributions made by animal models have been in the area of drug discoveries. Transgenic mice have been credited with facilitating the development of a number of effective targeted therapies for many fatal cancers like acute promyelocytic leukemia (APL) [20].

For burn studies, *in vitro* models are limited in their ability to capture all aspects of burn pathophysiology and the complex clinical features of human burn injury. For these reasons, animal models of burn are needed to uncover the post-burn pathological mechanisms and test novel therapeutic approaches. One of the major limitations in searching for practical treatment options for burn patients has been the lack of a suitable animal model that captures all of the prominent features of burn trauma. However, animal models are still essential for uncovering the molecular [21], [8] and cellular [22] aspects that characterize human burn traumas. In view of the heterogeneous nature of burns, a number of different animal models of burns have been developed as valuable tools to study the disease pathophysiology. In this review paper, we begin with a general discussion of relevant factors that can determine the clinical relevance and validity of animal burn models. We then briefly review some of the currently used animal models (small and large animal models) in burn research and discuss their clinical relevance to humans. This review also allows new researchers in burn trauma to survey the methods and temperatures that have been used by their peers to inflict a burn injury of a specific surface area in mouse or rat. Finally, we address the economics of animal research in burn models, discussing the apparent shift from using larger animal models to smaller ones.

Skin Histology Across Species

The ability of the skin to provide a barrier against the hostile external environment is a fundamental property of all species. However, there is tremendous diversity among the species in the structure and anatomy of the skin (Table 1). Knowledge about these histological differences in skin anatomy is critical if researchers want to have a close analog of the human skin.

Mouse

Although the mouse skin contains the major layers of human skin (epidermis, dermis), there are significant histological and physiological differences of these skin layers to that of humans. For instance, mouse have a thinner epidermis and dermis compared to humans [23], [11], and the interphase of human epidermis and dermis is highly undulated whereas in the mouse it is flat [23]. Also, mouse skin dorsum is covered with dense hair that undergoes a defined cycle of hair growth that is significantly different from as in human hair. For

example, the mouse hair cycle is usually three weeks, where as human hair cycles can last several years [23]. Additionally, mouse skin is unique in having a distinct panniculus carnosus (a thin skeletal muscle layer found only at the platysma of the neck in humans) [23], [24], [11]. Thus, these are important considerations one should factor in when assessing the translational accuracy of utilizing mouse in wound healing studies.

Rat

Rats and humans share physiological and pathological characteristics in many organ systems that have been already well established in literature. Similar to humans, the rat skin is also composed of the major layers (epidermis, dermis) of human skin. However, it does not perfectly mimic the human skin architecture because of its unique skin morphology. Rats have been classified as “loose skinned animals”, primarily because of their skin’s elasticity and its lack of a strong adherence to the underlying structures compared to humans [11], [24]. Such property of the rat skin plays a significant role in the wound healing of rats, described later in this review. The discrepancies between human and rat skin are also present internally, as rats possess the enzyme L-gluconolactone that converts L-gluconogammalactone to vitamin C, whereas humans lack this enzyme [24]. This is particularly relevant in wound healing as vitamin C plays a vital role in collagen synthesis and thus prevents the disease condition of scurvy [25]. The inherent differences between human and rat skin should be considered in determining whether rats are appropriate in wound healing models.

Pig

More recently, the pig has been extensively validated as a model for studying human skin because of its anatomical and physiological skin architecture closely resembling that of humans. The epidermis and dermis of the pig is thick, which is also the case in humans [26]. The pig epidermis ranges from 30 to 140 μm; similar to humans which ranges from 50 to 120 μm [11,26]. In addition, the skin of the pig is more firmly attached to the underlying structures like seen in humans. Also, both humans and pigs show resemblance in terms of hair coat (sparse, dense). Neither pigs nor humans have an extensive panniculus carnosus which is found in small “loose” skinned animals [23]. Even commonalities below the skin contribute to the list of similarities between human and pig skin. For example, the size, orientation, and distribution of blood vessels in the dermis of the pig are similar to blood vessels in human skin [26]. Other important similarities between pig and human skin include epidermal enzyme patterns, epidermal tissue turnover time, the keratinous proteins, and the composition of the lipid film of the skin surface [11]. These characteristics make the pig an ideal animal model for human-related validation of valuable research information.

The above anatomical and physiological differences between man and animal should be noted to improve the translation of preclinical findings into successful clinical applications since no animal model is a perfect representation of humans. In particular, the strengths of each animal model for biomedical research should be considered when addressing phenomena.

Stages of Wound Healing

The last few years have seen a renewed focus on the use of animal models to investigate the mechanisms of wound healing. Wound healing is a very complex and intricate process. This review is concerned with the repair of wounds in skin; we will not attempt to deal with the molecular factors involved in the healing process. In most species, the normal response to trauma occurs in three overlapping but distinct stages: of inflammation, proliferation, and re-epithelialisation/ re-modeling [27-29].

The immediate response to injury is mediated by damaged cells along the wound site. These cells transmit “stress” signals immediately to activate the inflammatory response. The priority of the inflammatory responses is to counteract microbial wound infections and this takes precedence over wound closure [29]. During this phase, pro-inflammatory factors like serotonin, bradykinin, prostagladins, prostacyclins, thromboxane and histamine are released into the local wound site [30,31].The goal of this initial phase is to re-establish tissue integrity and homeostasis. Once the necessary framework has been accomplished in the inflammatory phase the subsequent production of a new functional barrier is initiated in the proliferation phase [29].

The infiltration of the wound site by fibroblasts and other cell types initiates the proliferative phase [32]. The function of fibroblasts is primarily collagen deposition in the dermal wound area [27,29]. Increased production of Type III collagen and fibronectin occurs within the first 3 days after tissue injury [30]. This activates several signalling pathways that modulate healing [33]. Fibroblasts also secrete cytokines that attract keratinocyte cells to the injury site [31]. The keratinocytes function in re-epithelialising the wound site, ultimately restoring the barrier function of the epithelium [27], [29]. Concurrently with fibroblast and keratinocyte migration, angiogenesis also occurs. Angiogenesis, the formation of new blood vessels, is critical for wound healing since fibroblasts and epithelial cells require a continuous supply of oxygen and nutrients to function optimally [29]. The proliferative stage terminates with the breakdown of provisional extracellular matrix leading to a decline in hyaluronic acid and an increase in chondroitin sulfate which gradually triggers the fibroblasts to stop migrating and proliferating [27,33].

In the final stage of wound repair, the remodelling stage, collagen undergoes cross-linking to improve its strength and stability. However, as remodelling progresses collagen synthesis and collagen catabolism begin to take effect [29]. Imbalance in either excessive matrix synthesis or decreased matrix catabolism can lead to keloid [34] and hypertrophic scar formation [35,28]. As the extracellular matrix is reorganized and remodelled, newly formed blood vessels continue to mature and form functional vascular networks. Depending on the wound size, the remodelling phase can last anywhere from weeks to years [29].

The wound healing cascade is far more complex than briefly discussed here with a number of questions still unanswered. Studying wound repair in animals could improve our understanding of wound repair in humans. Therefore, an accurate animal model that closely mimics the three overlapping phases of wound healing would enable investigators to study each phase more precisely. More importantly, an accurate animal model would also

facilitate the screening of potential treatments and interventions. However, there are number of limitations to how closely one can replicate the wound healing process of humans in animals. Many animals resemble the wound healing process of humans closely; some do not even come close, making the extrapolation of any findings to humans very difficult. Several models of burn/wound healing in animals in literature will be evaluated. A summary of these models is outlined below.

Wound Healing Across Mammals

Among the animals, amphibians are unmatched in their healing and regenerative capacities.Upon injury, these animals regenerate an impressive array of new body parts, such as limbs [36]. These particular aspects of the amphibians have been exhaustively reviewed elsewhere [36,28] and will not be the focus of this review paper. Instead we will limit our discussion to the most commonly used animals in wound healing studies; the mouse, rat, and pig.

Mouse

The mouse is one of the most used animal model in studies involving burn and wound healing. As a research model, this animal has provided researchers with key insights into the signalling pathways involved in the healing process, in large part due to the variety of mouse-specific reagents and transgenic feasibility in mouse. Also due to a substantially reduced healing time [23], and superior immune system [37], the morbidity of mice in research is quite low. Although the mouse model has its specific advantages, its major drawback is its failure to completely mimic the wound healing process of humans. Mouse wound healing occurs primarily through wound contraction [23], [11] which makes healing time of mouse quite rapid. In contrast, humans heal primarily through re-epithelialisation and granulation [27], [29]. Another potential hindrance in utilizing mice to study wound healing is that unlike humans, mice are not subject to hypertrophic or keloid scar formation [23]. Moreover, mouse skin is covered with dense hair. As hair follicles are rich for progenitor cells, mouse skin might have an enriched pool of progenitor cells which facilitates rapid skin healing and keratinization [38-40]. Since the skin is the first line of defense, it is populated by a group of antimicrobial peptides known as the defensins. These peptides play an important role in preventing the localization of pathogens in the skin, particularly in situations where the skin barrier is compromised [41],[42]. Neutrophils are the main source of leukocyte defensins in humans, but defensins are not expressed by neutrophils in mice [37]. Differences also exist in both innate and adaptive immunity between humans and mice that are critical for adequate wound closure during burns. For instance, toll receptors, inducible nitric oxide synthase, cytokines and cytokine receptors, helper T-cells (Th1/Th2) differentiation, and antigen presenting function of endothelial cells all show interspecies difference [37]. Perhaps, the most noteworthy differences between murine and human systems are those involving chemokines and chemokine receptors. Currently, the chemokines IL-8 (CXCL8), neutrophil-activating peptide-2 (CXCL7), inducible T cell chemoattractant (CXCL11), and monocyte chemoattractant have been identified in humans but not in mice [37],[43]. These chemokines are critical for wound repair as they contribute to the regulation of epithelialization, tissue remodeling, and

angiogenesis [44]. In fact, chemokines have dual effects in wound repair as they integrate inflammatory events and reparative processes [44]. Thus, distinct wound healing processes (wound contraction) and differences in immunity and chemokine expression should be considered when trying to extrapolate any findings from mouse studies to humans.

Rats

Similarly, rats have been frequently used in burn studies primarily because of cost considerations. Despite their popularity, the wound healing mechanics of rats is substantially different than that of humans. Wound contraction is considered to be the primary healing method of rats as opposed to re-epithelialisation seen in humans [24]. This is because rats, like mice, possess a subcutaneous panniculus carnosus muscle that facilitates skin healing by both wound contraction and collagen formation [23],[24]. Since wound contraction is rapid the overall healing time of rats is substantially reduced, unlike with re-epithelialisation which involves the creation of new skin tissue [24]. As such they are less prone to systemic sepsis [11] and immunosuppression [3] seen in larger animals, as their wounds heal much quicker. The reduced healing time in rodent burn models allows researchers to quickly study the mechanics of wound healing.

Pigs

Wound repair in pigs has been the focus of recent excitement because of the relatively close relationship it shares with humans. Aside from the pig skin architecture being similar to that of human skin, the healing process of pigs and humans occur through physiologically similar phases (inflammation, proliferation, re-epithelialisation and re-modelling) [26],[27]. Additionally, the pig has firmly attached skin to the underlying structures making wound healing occur precisely in the same manner as seen in humans [26]. Aside from the aforementioned similarities, the pattern of vascularisation of pig skin differs somewhat from human skin. Pigs display a lower, mid-dermal and sub-epidermal network, where the latter is less dense than seen in humans [26,45]. The exact timeline of wound healing in pigs and humans is quite variable due to a number of factors like wound size, cause of injury [46], healing conditions, and overall health status. Generally speaking however, scalding burns in pigs heal typically by 21 days [47] with re-epithelialisation occurring between 7-14 days [45] post wound infliction[47]; similar timelines have also been observed in humans. For optimal wound closure, a number of growth factors are released during the complex phases of inflammation, proliferation, and remodelling. Some of the most important of these growth factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF-BB), and transforming growth factor-β1 [48]. Analysis of these growth factors in pigs has revealed similar patterns of expression and concentration during wound healing to humans [48]. In fact, like humans, pigs show age-related delay in healing that has been linked to delayed and diminished growth factor release. Despite the advantages of the pig wound model, cost-benefit considerations show that they are challenging as they have a greater risk of infection, demanding greater care and expenditure [11]. Pigs also tend to have a greater morbidity when compared to smaller animals; because of their size they are more prone to wound infection putting them at risk for sepsis.

Given that no single animal is the perfect model for all biological contexts, a superior approach would be to integrate the information derived from multiple model systems. Because each animal model of wound healing has its own advantages and disadvantages, the field stands to gain from the integration of the molecular and cellular knowledge garnered from these organisms. The study of hypermetabolism [8,10] and sepsis [11] in burn patients serves as an example of how the integration of data across multiple animal models has informed us on the pathophysiology of burn traumas in humans. The mouse model with its well characterized immune system [37] has helped inform our understanding of the suppression of cell-mediated immune responses post-burn and the increased susceptibility to subsequent septic complications and mortality [11]. Moreover, using cell lineage studies, mouse models enlighten the stem cells movement to healing bed in context of regenerative studies [32]. Conversely, lack of scar formation in mouse wound healing models [23] has pushed investigators to use the pig model to uncover the mechanisms behind hypertrophic and keloid scar formation in burn patients. Thus, the aforementioned animals have each contributed significantly to uncovering the biological process and diseases affecting the human skin.

Post Burn Hypermetabolism

A hallmark of burn injury is a hypermetabolic response that results in significant pathological alterations in a number of tissues. The source of this hypermetabolic response is currently not well defined but likely involves increases in glucocorticoid, catecholamine, and glucagon secretion post-burn injury [10]. The primary goal of this response is to provide sufficient energy for maintaining organ function and whole body homeostasis under demanding trauma conditions. Prolonged hypermetabolism becomes detrimental and is associated with vast catabolism, multi-organ failure, and death [49]. These alarming situations increase the priority for developing animal models to investigate the underlying pathophysiological events that serve to determine the catabolic state and its related comorbidities. Thus, this section summarizes various animal models that are used as tools in burn related metabolic research and critically evaluates the physiological similarity of the models to the human condition.

Currently, there are two opposing explanations of the cause of the hypermetabolic response following thermal injury. One school of thought suggests that the increase in heat production is a thermoregulatory adjustment by our body to compensate for the increased rate of evaporative heat loss across the surface of the burn wound [50],[51]. In contrast, others suggest that the hypermetabolic response is a reflection of the increased energy costs of the injury [51]. They further argue that the metabolic drive is sensitive to, but independent of, alterations in thermoregulation. Thus, resolving these two opposing thoughts hampers on the development of an appropriate animal model of burn.

Small Animal Models of Burn Hypermetabolism (Mice and Rats)

The ability to introduce or eliminate genes to or from the genome of rodents, their larger family size, formalized pedigree structure and easy measurements of their phenotype parameters have truly made rodents a reliable animal model for burn research. However, if

the notion that the hypermetabolic response post thermal injury is purely a thermoregulatory adjustment, then findings and data collected from small fur bearing rodent burn models must be questioned and may be untrustworthy. This is because rodents have a dense hair coat that affords them insulation and thereby limits heat loss through the skin post-burn injury [52]. In addition, unlike human patients, when rodents are challenged with 30% total body surface area (TBSA) burns, from our own observations their metabolic response is resilient to a degree that 24 hours after burning, these animals are very active and resume normal eating patterns. Even if we were to entertain the opposing view that the hypermetabolic response post-burn injury is due to the demanding energy costs of the injury, these small animals still fail to fully recapture the metabolic alterations seen in humans post-burn. Since inflammation, insulin resistance, muscle wasting and hyperglycemia are central characteristics of the post-burn response in humans, it is imperative that the animal model can mimic such pathological alterations [6]. Small animals like the mouse and rat are generally not ideal models of metabolism research in burns since their metabolic profile is significantly different from that of humans. For instance, rodents typically have low levels of total cholesterol (TC) and density lipoprotein-cholesterol (LDL-C) but high levels of high density lipoprotein-cholesterol HDL-C, whereas the reverse is true for humans [53],[54]. Rodents lack the plasma cholesteryl ester transfer protein (CETP) which causes the contrasting cholesterol profile and, therefore, about 70% of the plasma TC is found in HDL particles [53]. The ability of rodents to maintain their cholesterol profile when challenged with high fat diet presents major problems in conducting research to uncover the mechanisms behind impaired insulin secretion and impaired insulin action, which is a phenotype of the hypermetabolic response post-burn. In fact, when these small animal models are artificially pushed to develop a diabetic phenotype with its associated hyperlipidemia, they still fail to display the same islet pathology as humans with type 2 diabetes (T2D) [53]. In this context, researchers working with mice have turned to populating human hepatocytes in mice to study human liver mediated metabolism [55]. Thus, there are stark metabolic and physiological differences between humans and rodents, and these differences have undoubtedly slowed progress and complicated the translation of findings into effective intervention therapies for burn injury and its debilitating effects. Despite all these disadvantages, rodent models of metabolic diseases like diabetes and obesity have had a substantial role in furthering our knowledge about the pathology of these two conditions. For instances, the leptin receptor deficient mouse model (db/db) has substantial role in progression of our knowledge about diabetes and used for drug studies [56].

Large Animal Models of Burn Hypermetabolism

Large animals, such as pigs and rabbits, are emerging as the animal of choice for burn related research as their size facilitates the study of the systemic effects of burns. In fact, studies have shown that larger animals inflicted with a 25% TBSA burn generates a hypermetabolic response greater than smaller animals and closer to that seen in human patients [57],[58]. These larger animals also serve as attractive biomedical models for studying energy metabolism because they are devoid of brown fat like humans [53],[58]. This is an important consideration because brown fat has the ability to regulate energy balance and other aspects of energy homeostasis. In addition, the pig has similar metabolic

features and responses to burn injury as humans [59]. For instance, it has been shown clinically that severe injury results in hepatic dysfunction and fat deposition in the liver of burn patients [13]. Porcine models have been useful in this regard, as it has been shown that they also present with similar phenotypic alterations such as hypertrophic adipocytes and fat deposit in the liver post burns [60]. Moreover, researchers have turned to larger animals because proportionally these larger animals have similar organ sizes to humans [53]. This is critical as the larger size can allow multiple assays to be carried out in adipose and muscle tissue without pooling multiple animal samples together [53],[57]. While the pig model is superior in its ability to capture most, if not all, the pathological alterations post-burn seen in humans, the high expense of housing and complicated burn procedures have limited the use of this model.

Animal Models of Burns

Our complete understanding of the molecular, cellular, and pathophysiological alterations governing burn injury has not been fully elucidated. To gain a comprehensive understanding of the mechanisms of hypermetabolism and sepsis seen in burn patients, there is a need of an animal model that adequately mimics these pathological states. Perhaps the most critical factor of clinical relevance is the method used to induce burns in experimental animals. Techniques that have been used to generate burn surfaces in experimental animal models include direct contact with a heated metal [11],[61], electricity [62] and heated water [11]. In the direct contact method, the back of the animal is shaved and a heated metal is applied to the skin as many times as necessary to induce the desired burn surface area [11]. In burns achieved through metal instruments, the area and temperature used vary according to the shape and size of the instrument. The drawback of this method is the lack of a homogenous uniform burn depth. Electrical burn models are very complex to perform and usually require larger animals like monkeys to achieve lesions comparable to those observed in humans [62]. Among the aforementioned models, the hot water model has gained widespread use and is considered by some experts as the standard for animal models of burns. Burns caused by hot liquids are the most frequent cause of burns in children and the elderly [1,63]. Unsurprisingly, a standardized burn model involving the use of hot water in animal experiments has been developed. Below we explore further the hot water method in relation to its use in rodents (mouse, rat) and larger animals (pig). We will not discuss the electrical and direct contact burn methods further, as there is great variability among the techniques used and as such no standardized models currently exists for these methods in burn animal studies.

Standardized Scalding Burn Model in Mouse

Generally, the model involves the use of small (6-8 weeks old) healthy mouse. Initially, the mouse is anaesthetized through intraperitoneal injections of Ketamine and Xylazine or other anaesthetics [64]. In some instances, the mouse also receives 1 ml of saline subcutaneously along the spine to cushion the spinal cord from any injury [64]. Following this, the hair on the dorsum is shaved off to ensure even burn wounding. The dorsum is an ideal choice because it is difficult for the animal to reach and as such prevents further injuries to the wound area. The mouse is then placed on its back in a template constructed of a plastic

flame resistant mold (Figure 1A-D, Supplementary Figure 2) with the window exposing a predetermined surface area of skin [65]. The exposed area of the mouse from the template is then immersed in a 100°C water bath for 8 seconds to inflict a full thickness burn [64] (Figure 1A-D). The animals are then observed frequently for signs of pain or discomfort and treated with buprenorphine or other pain killers as needed. The temperature (60-100°C) and exposure time (8-12 seconds) [11] vary from study to study (Table 2). The described procedure has been proven experimentally by our laboratory to inflict a full thickness burn (Figure 1F). In mice one is limited by size and since they can only tolerate a 30% TBSA burn. However, clinically speaking the hypermetabolism phase is not fully activated in burn injuries of less than 40% TBSA [66]. Thus, while the mouse burn model is simple and straightforward, it loses significance when it comes to studying the complex post-burn etiology of hypermetabolism.

Standardized Scalding Burn Model in Rat

Similarly, the rat scalding burn model is straightforward and is achieved exactly in the same manner as that of the mouse model, with some minor differences such as the temperature and length of exposure to the heated water (Table 3). Also rats which are larger can handle up to a 60% TBSA burn, by using the aforementioned model on the dorsum of the rat and incorporating another wound to their abdominal region. By our experience, inflicting a burn wound of greater than 60% TBSA in rats results in reduced survivability and is not sustainable for experimentation. Another consideration relates to the need to have a burn injury model of sufficient magnitude to cause hypermetabolism observed in human burns with high TBSA. During the early post-burn phase in humans, hyperglycemia occurs as a result of an increased rate of glucose appearance along with an impaired tissue extraction of glucose, leading to an overall increase of glucose and lactate [67]. Therefore, while the rat burn model is superior to the mouse in its ability to recapture hypermetabolism, it becomes complex when one tries to incorporate an infection feature to this model to replicate the post-burn sepsis seen in patients with greater than 60% TBSA.

Standardized Scalding Burn Model in Pigs

As discussed, of all animal species, the pig's skin most closely resembles that of humans [26]. The pig burn model is basically a replicate of the rodent model except for some minor technical changes to reflect the size of the pig. Initially, the pig is sedated with intramuscular injections of Ketamine and Azaperon [68,69]. Then, the pig is put under a surgical plane and intubated by receiving pentobarbital and ketamine [68]. After surgical preparation the back hair of the pig is clipped with hair clippers and then the pig is stabilized in a special device exposing a predetermined surface area of skin [11,68]. A water tank containing boiling water is circulated over the area to be injured for a specified time, usually seconds [70] (Supplementary Figure 2).The method for sedation, induction of anaesthesia and pain control, especially in the postoperative period, varies from study to study and depends primarily on the severity of the burn injury inflicted. The main advantage of this model is the ability to inflict greater TBSA burns than the rodent model, facilitating research on the mechanisms behind hypermetabolism and sepsis in burn patients. Most studies have not used a burn wound greater than 45% TBSA in pigs, suggesting this range is sufficient to

elicit the activation of the pathological pathways seen clinically in humans. Due to the size of the animal involved, the pig burn model can be quite challenging to execute and can pose a risk of burning to the researcher.

Rabbit

To resolve the complexities and high costs associated with the pig burn model while maintaining the metabolic relevance to humans, researchers have pioneered the rabbit burn model [57]. Rabbits are an appropriate animal model for studying hypermetabolism and its pathological alterations in energy homeostasis because they share with humans several aspects of metabolism, such as similarities in composition of Apo lipoprotein B (Apo B) containing lipoproteins, hepatic production of Apo B 100-containing very low dense lipoproteins (VLDL), human-like Apo B, and low hepatic lipase activity [53]. Unlike, the rodent models, the rabbit model facilitates opportunities to conduct systemic effects of burn injury like muscle wasting through the feasibility of primed constant tracer infusion studies to investigate dynamic changes in whole body amino acid and substrate metabolism [57]. Furthermore, the larger tissue mass (liver, muscle) of the rabbit allows *in vivo* imaging studies that investigate the aspects of whole body glucose and amino acid metabolism in response to thermal injury [57]. It has also been shown that rabbits present with elevated REE (resting energy expenditure) levels post thermal injury, which is a characteristic metabolic feature in burn patients [57]. Finally, since protein metabolism and muscle wasting are hallmarks of burn injury, animal models that re-capture these clinical features of burns are critical to understanding the cellular mechanisms deregulated in these pathological states. The rabbit burn model has proven to be useful in this regard, as studies have reported that leucine an important amino acid involved in muscle anabolism, shows similar kinetics and pattern of change post thermal injury to that observed in human patients [57,71]. Conducting a rabbit burn model is quite straightforward as it follows the same techniques and procedures outlined in the standardized mice burn model. Because of differences in skin thickness, the rabbit is immersed in the boiling water for 10 seconds or longer to ensure full thickness burns [57].

In summary, when it comes to deciphering the systemic and cellular mechanisms involved in the hypermetabolic response to burn injury evidence supports the use of larger animals. This has been due to the ability of these larger animals to demonstrate a pattern of alterations in overall aspects of whole body energy metabolism, protein, and carbohydrate metabolism similar to that seen clinically in burn patients.

Modeling Inhalation Injury in Animals

Although genetic and cost considerations have underpinned the growth of rodents and other small animals in burn research, an exciting emerging area in burn research is the use of sheep to model inhalation injury following burns [72,73]. Inhalation injury constitutes the bulk of fatalities in burn centers around the world and has a complex etiology, varied patterns of onset and clinical manifestations [74]. An animal burn model that captures the complexities of this burn injury will help to facilitate the development of effective clinical therapies that can reduce the high mortality rates associated with this specific type of

thermal injury. Although this type of injury has been studied in smaller animals like rodents, the sheep has been recognized as being the gold standard in studying this injury [75]. No other animal models comes close to the superiority of the sheep in recapturing the clinical, physiological, and histological alterations seen in smoke induced inhalation injuries observed in humans [75]. For example, like seen clinically in humans, sheep also present with histological changes of the respiratory tract that include disruption and loss of cilia and loss of respiratory epithelium post inhalation injury [75]. Animal size is another important consideration in selecting appropriate animal models to investigate inhalation injuries because physiological parameters such as arterial oxygen tension and mean arterial pressure are monitored in this type of injury [72]. It is easier to obtain sufficient quantities of blood or plasma from larger animals to elucidate the pathological alterations of inhalation injury on blood gases, plasma cytokines, and leukocyte counts over time [73]. The sheep provides not only an adequate body size to conduct such research, but the model is easily reproducible [75]. Furthermore, clinical studies have implicated nitric oxide (NO) in the involvement of pathogenesis of inhalation injury [72]. Given this finding it is important to consider the important species dependent differences in NO pathways. Specifically, the production of NO during innate immune-mediated response to *Mycobacterium tuberculosis* differs across species. For instance, human macrophages produce very low amounts of NO, whereas rodent macrophages produce large amounts of NO [72]. Macrophages of sheep, monkeys, and pigs are closer to human macrophages and generate little NO [72,76]. Other advantages that have made the sheep a popular model for studies in inhalation injury include: low cost, innate hardiness, and tolerance to surgical and chemical manipulation. No single animal model reproduces all the characteristics of human inhalation injury; nevertheless, the sheep model has been quite successful in reproducing some of the clinical manifestations of this injury.

Trends in Animal Research

In hopes of getting a better understanding of the changes that have occurred in the animal burn model, we have examined some trends that have occurred in animal research over the decades. Scientific papers were identified from the period of 1960 to 2012. The research was performed using the database PubMed. The main keywords used were: “animal models AND burns AND rat”, “animal models AND burns AND mouse”, and “animal models AND burns AND pig”. By applying such norms and procedures, thousands of papers were identified and some apparent trends were noticed.

In the early 1960s, the rat was the choice of species in burn studies (Figure 2A). With time, however, investigators found that the rat model was insufficient in helping to identify the specific pathological molecular pathways activated during burn trauma. In response, the burn rat model was modified to create the burn mouse model. With the vast abundance of disease models, transgenic tools, knockout strains, and mouse specific reagents the burned mouse model has over taken the rat burn model in popularity over the last decade (Figure 2A). While the pig burn model has increased in popularity in the last few decades, the trend seems to indicate the pig will continue to lag behind the rat and mouse in the years to come (Figure 2A). Perhaps it is attributed to their high economic cost and special post-operative care requirements. Thus, it is not clear what directions the burn model will take. Regardless

of the path that burn research takes, the fundamental rodent model will continue to play a robust role in this field.

Economic Considerations

Ideally, animal research models should be driven by maximizing their translational relevance to humans, rather than by economic considerations [77]. To some researchers, the reduction of budgets available for medical research programmes is a sobering constraint and makes the potential benefits of utilizing higher order animals with high costs in testing their hypothesis a low priority. Instead it is about the most cost-effective allocation of incremental changes in resources. To them, the squeeze on funding is a cue to look for ways to drive large reductions in the need for costly animals, as a result jeopardizing the clinical relevance of their findings to humans. In Figure 2B, we highlight the economic costs associated with some of the frequently used animals in burn research in order to guide discussions about choosing the correct animal model. For instance, the pig is an animal which shares several characteristics such as metabolism and skin histology with humans; however, cost analysis reveals that they are more expensive (Figure 2B). Conversely, while small mammals like the rat and mouse are inexpensive, this gain is quickly lost to their lack of human relatedness. These important economic concerns are rarely addressed in scientific papers using animal models. Nevertheless, incorporating these economic factors into the selection of the appropriate model is an important area of ongoing and future research to help inform the decision-making processes.

Summary

In vivo burn models have contributed to our understanding of the physiological and pathophysiological mechanisms associated with this devastating trauma. One of the major barriers in extrapolating these findings to humans is that, owing to ethical and financial constraints, researchers rarely utilize large animal models that are clinically relevant. In either case, the molecular mechanisms gleaned from these studies will help to identify novel treatment strategies that may be translated into the clinical scenario. None of the three main animal models of burn described in this review can be considered superior to one another; rather they are best viewed as complementary. While animal research holds great promise in biomedical research, some animal models have recently been put to question as new findings have shown that the mouse model poorly mimics the genetic and proteomic responses of human inflammatory diseases [78]. As such, translational research is always necessary to address systemic diseases while animal models may pave the road to mechanisms. Despite their limitations, the rational utilization and application of animals will remain one of the most useful tools to help uncover the pathology behind burn trauma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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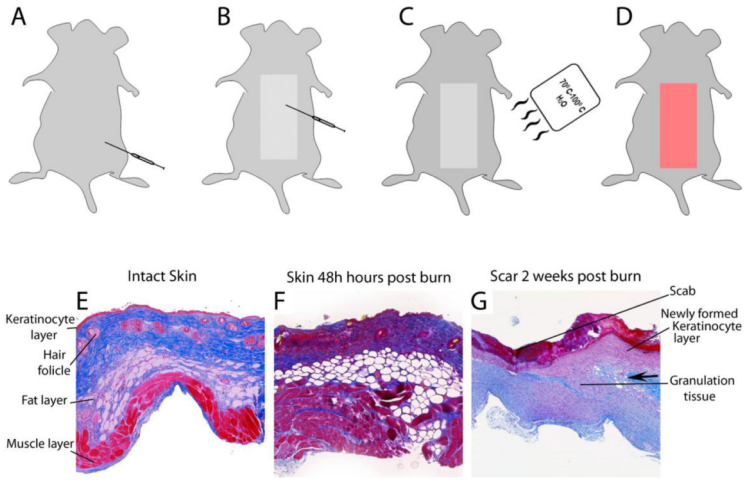

Figure 1. Experimental steps in the burn rodent model and histological images of C57/BL mice skin subjected to full thickness burn (30%TBSA)

(A) The rodent is anesthetised with an intraperitoneal injection of Xylazine and Ketamine. (B) The area (dorsum) to be burned is shaved with a clipper to ensure an even burn. (C) Rodent is then placed in a flame resistant mold with an opening exposing a pre-determined total body surface area to burn; the exposed area is then immersed in a 100°C water bath for 8 seconds. (D) Lactated Ringer's solution is then administered intraperitoneally for resuscitation; buprenorphine or other analgesia may be administered subcutaneously for pain control. Excised burned skin tissue specimens from burned mice (thickness=5μm) were harvested and then Masson's trichrome staining performed (E) Intact skin showing histological component of mouse non-burned skin. (F) Burned skin harvested from mouse 48h post burning. Note that animal presenting with complete destruction of skin, most obviously in the epidermal/dermal segments. (G) Animal at 2 weeks post-burn showing signs of wound healing; re-epithelialization (at wound edge), neovascularization, and formation of new granulation tissue. Arrows indicate wound edges or new granulation tissue formation. Collagen fibers in the dermis are stained in blue, epidermis and muscle stained in red.

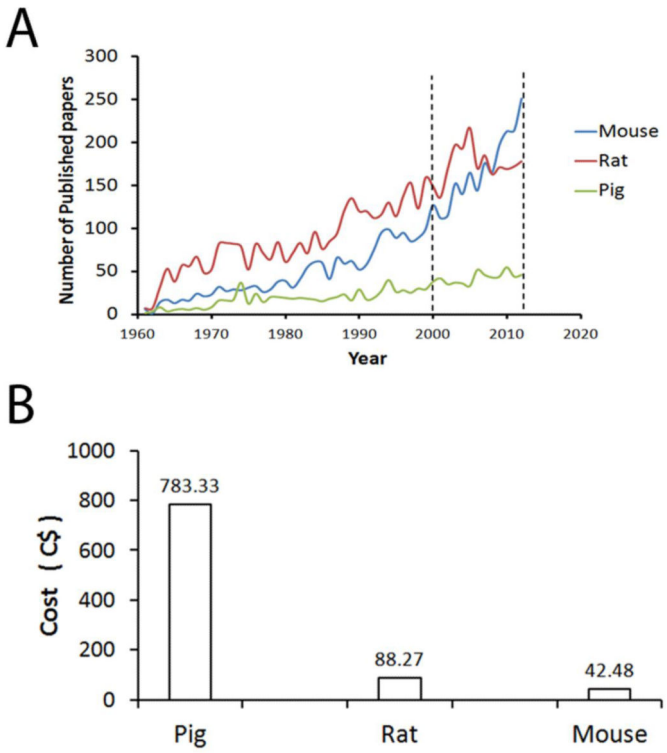

Figure 2. Trends and Costs Associated with Animals in Burn Research

Illustration of the total number of articles appearing in the PubMed database for each species by year of publication. (A) The popularity of the rat as the species of choice in burn studies during the last century declined in the mid-2000s when the mouse research overtook the amount of burn research in rat. (B) The graph shows the cost of purchase, delivery, and housing for 30 days of a pig, rat, and mouse used in burn research (in Canadian dollars). Costs were calculated based on the quotes and housing fees of the animal facility here at Sunnybrook Health Sciences Centre in Canada. Precise costs will differ from one facility to another; however, the trend remains the same with regards to inter-species cost differences.

Table 1

Skin Histology Across Mammalians

Trait	Human	Pig	Rat	Mouse
Hair Coat	Sparse	Sparse	Dense	Dense
Epidermis	Thick	Thick	Thin	Thin
Dermis	Thick	Thick	Thin	Thin
Panniculuscarnosus	None	None	Present	Present
Skin architecture	Firmly attached	Firmly attached	Loose	Loose
Wound Healing Mechanism	Re-epithelialisation	Re-epithelialisation	Contraction	Contraction

Table 2

Size of Mouse Scald Burn Model

TBSA %	Species	Temperature (°C)	Length of Exposure (Seconds)
2.5	Mouse	54[79]	25[79]
7	Mouse	65[80]	45[80]
10	Mouse	65[81]	20[81]
18	Mouse	90[82]	9[82]
15	Mouse	85[83] 95[84,85] 100[86-90]	9[83] 7-8[84,85] 7-8[86-90]
20	Mouse	90[91-93]	7[91-93]
25	Mouse	90[94,95]	9[94,95]
30	Mouse	90[96] 95[97]	9[96] 6[97]
35	Mouse	80[98] 97[99-101]	15[98] 7-10 [99-101]

Table 3

Size of Rat Scald Burn Model

TBSA %	Species	Region (Dorsum/Ventral)	Temperature (°C)	Exposure Time (Seconds)
10	Rat	Dorsum	80 [102]	10 [102]
15	Rat	Dorsum	95 [103]	8 [103]
20	Rat	Dorsum	60 [104] 80 [105] 90 [106] 100 [107]	25 [104] 6 [105] 10 [106] 10 [107]
30	Rat	Dorsum	60 [108,109] 90 [110],[111] 92 [112] 97 [113] 98 [114-117] 100 [119] 106 [120]	40 [108] 27[109] 10 [110] 20 [111,112] 10 [113] 12 [114-117],15 [118] 30 [119] 9 [120]
35	Rat	Dorsum	100 [121]	15[121]
40	Rat	Dorsum Ventral	100 [122-124]	10 [122-124] 2 [122-124]
45	Rat	Dorsum Ventral	87 [125]	10 [125] 3 [125]
55	Rat	Dorsum Ventral	80 [126]	15 [126] 8 [126]
60	Rat	Dorsum Ventral	96 [127]	10 [127] 2 [127]
		Dorsum Ventral	98 [67,128]	10 [67,128] 2 [67,128]