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PLGA polymer: From a classic drug carrier to a novel therapeutic activity contributor

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ABSTRACT

Poly Lactic-co-Glycolic Acid (PLGA) is well known for its biocompatibility and minimal toxicity. It is one of the most promising biodegradable polymeric drug delivery systems in nanotechnology able to get endorsement from regulatory bodies to enter market. For many decades, PLGA has been functioning as an excipient, which by definition should not have therapeutic effects at a given dose of formulation. Lactate (one of the hydrolysis products of PLGA) has a key role in biochemical pathways and could improve physiological activities in certain illnesses by exerting therapeutic effects such as angiogenesis and promotion of healing. These activities however depend on the released amounts and metabolic clearance of lactate and route of formulation delivery. In the current paper, along with several key notes on the lactate interactions, we would like to inform the PLGA research community that lactate (resulting from local delivery of physiologically significant amount of PLGA) may positively or negatively affect therapeutic efficacy of certain drugs. Hence, the excipient role of PLGA should be investigated for newer dimensions to unveil its pharmacological contributions in some biomedical applications.

1. PLGA –widely used polymeric excipient in medical applications

Since its inception in 1970's poly (lactide-co-glycolide) (PLGA), an aliphatic polyester, has always dominated the co-players due to its broad and unique physicochemical and biomedical applications. Kapoor et al. and Martins et al. discussed in detail the exceptional properties of PLGA and its wide use in medical applications, nanotechnology and tissue engineering [1,2]. Chemically PLGA is a block *co*-polymer of polylactide (PLA) and polyglycolide (PGA); upon degradation, it produces byproducts lactate and glycolate, which can respectively, feed the Krebs' cycle and gluconeogenic pathways, or be oxidized before transamination or excretion, hence, the high biocompatibility and low toxic nature of PLGA. Feasibility to alter chemical properties of PLGA such as monomer ratio of lactic acid and glycolic acid (LA: GA), crystallinity, and molecular weight, led to produce different grades of PLGA. Molecular weight and LA/GA ratio (GMP grade commercially available combinations - 50:50, 65:35, 75:25, 85:15) influence different properties of PLGA such as solubility, inherent viscosity and glass transition temperature, which are critical for tensile strength, and flexibility of polymer chain. Ester or acid terminations and other chemically active groups along the polymer chain aid not only in hydrolysis process but also in surface functionalization with active molecules [3]. For example, PLA with 100% LA degrades 2 times slower than PGA (100% GA) [4].

Several hundreds of published articles and patents reported different types of PLGA or PLA based drug delivery systems (DDSs) such as nanoparticles, microparticles/spheres, implants, nanogels, nanofibers, rods, thin films, supporting matrices and combinations of these DDSs [1]. The loaded cargos and formulated PLGA delivery systems ranged from small molecules to large proteins, hydrophilic to lipophilic, single to multiple molecules and simple to complex targeting systems [5]. Due to the commercial availability of GMP PLGA, versatility in degradation properties and surface modifications, sustained/controlled drug release and biocompatibility, PLGA drug delivery systems have been successfully passing different clinical trials of various ailments [6]. Recently filed patents are highlighting the commercial use of PLGA DDSs in different formulations. Singh et al. published a review with all the patents of formulations that directly used PLGA as main component [7]. The main challenges associated with PLGA DDSs are incomplete release, burst release, low drug loading, fast elimination, stability issues of encapsulated drugs and unavailability of robust manufacturing techniques [8]. However, different alternatives and mitigations have

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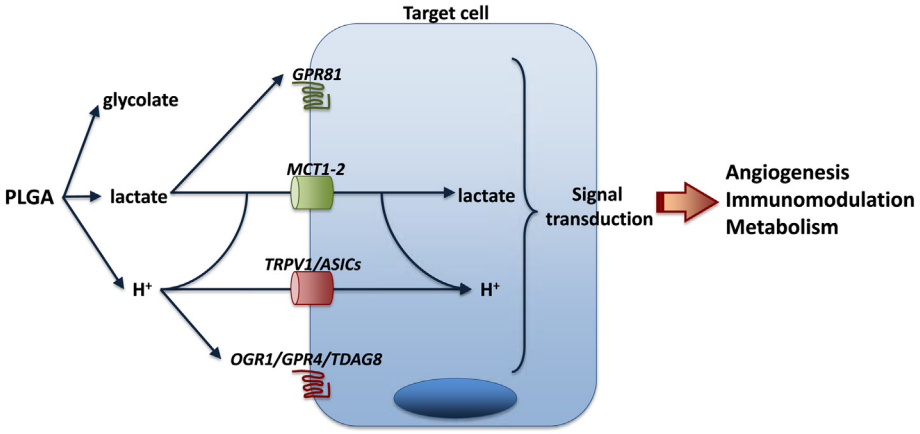

Fig. 1. PLGA exert biological effects through its degradation products.
PLGA hydrolysis releases glycolate, lactate and H^+. Lactate and H^+ sensing machinery include G protein-coupled receptors (GPR81, and OGR1, GPR4, TDAG8, respectively) and ion channels (MCT1, MCT2, and TRPV1, ASICs, respectively; MCTs co-transport both lactate and H^+). Lactate and H^+ release leads to the activation of effectors of signaling pathways regulating *e.g.* angiogenesis, immune system and metabolism.
Abbreviations: GPR: G-protein coupled receptor, OGR: ovarian cancer GPR, TDAG: T-cell death-associated gene, MCT: monocarboxylate transporters, TRPV: transient receptor potential V, ASIC: acid-sensing ion channels.

been developed to counter the previously mentioned drawbacks. With the available literature, one must agree that PLGA has been one of the most widely used biodegradable and biocompatible drug delivery systems in Nanomedicine [9–11].

A few research articles described that PLGA could alone improve physiological activities in certain illnesses by exerting therapeutic effects. All these reported therapeutic activities of PLGA can be appended to the hydrolysis products of PLGA lactate, glycolate, and H^+. We will recapitulate their respective roles within cell signaling (Fig. 1) in the following sections.

2. Role of lactate in metabolic and signaling pathways

Whereas a biological activity of glycolate has not yet been identified to our knowledge, L-lactate (hereafter lactate) is a rather well characterized active signaling molecule in many biological processes and signaling pathways. Lactate is the end product of anaerobic glycolysis under hypoxic conditions and of aerobic glycolysis occurring in rapidly dividing cells, *e.g.* during embryogenesis, cancer, wound repair and immune response [12,13]. In turn, the released lactate acts as a metabolic fuel for specific cells and as a chemical messenger [14,15]. The lactate-sensing machinery includes the monocarboxylate transporters (MCT) 1 and 2, both of which allowing lactate uptake [15], and the recently identified lactate-binding G-protein coupled receptor 81(GPR81) [16]. On the one hand, lactate uptake is followed by its oxidation into pyruvate, which, in turn, can inhibit prolyl-hydroxylase 2 (PHD2), a repressor of hypoxia-inducible factor 1 (HIF-1) [17,18] and nuclear factor κB (NF-κB) [19]. In endothelial cells, lactate-induced activation of both transcription factors stimulates the expression of pro-angiogenic factors interleukin 8 (IL-8) and vascular endothelial growth factor receptor 2 (VEGFR2) [17,18]. Lactate oxidation into pyruvate also consumes NAD^+, a cofactor necessary for (poly)ADP-ribosylation of proteins. The subsequent reduction of protein (poly)ADPribosylation increases the activity of pro-angiogenic vascular endothelial growth factor (VEGF) [20] and stimulates collagen deposition [21]. Those biological effects of lactate were observed at a concentration of 10 mM in cultures [18–20].

On the other hand, some effects of lactate are independent of its uptake and result from the stimulation of its membrane receptor. Stimulation of GPR81 results in a decrease of cAMP levels and can activate a non-canonical, β-arrestin-dependent signaling pathway [14]. EC50 value of lactate for its receptor is estimated at 5 mM. [22] In cancer cells, stimulation of GPR81 upregulates the expression of the pro-angiogenic factor amphiregulin [23]. At a physiological level, lactate released in the blood by exercising muscle has been shown to support VEGF release and angiogenesis in the brain through stimulation of pericyte-like cells expressing GPR81 [24]. Apart from its role in angiogenesis, stimulation of GPR81 inhibits lipolysis in fat tissue [16,22], maintains mitochondrial function and size of muscle cells [25,26] and downregulates the expression of inflammatory cytokines in macrophages [27,28]. Altogether, lactate stimulates angiogenesis and collagen deposition, influences metabolism, and modulates the immune response.

Independently of lactate, local extracellular acidification arising from PLGA hydrolysis [29] could further contribute to its biological effects. The H^+-sensing machinery includes include H^+ channels, such as transient receptor potential V1 (TRPV1) and acid-sensing ion channels (ASICs), and H^+-sensitive G protein-coupled receptors, such as ovarian cancer GPR 1 (OGR1), GPR4 and T-cell death-associated gene 8 (TDAG8) [30–32]. Whereas the first ones are thought to respond to a strong extracellular acidification, the latters are more sensitive to small variations of extracellular pH. Important and prolonged acidification might lead to significant cell death, but moderate acidification has a signaling function. In particular, in cancer cells and human mesenchymal stem cells, extracellular acidification (pH 6.6) was shown to induce the release of pro-angiogenic factors VEGF and IL-8 through the activation of transcription factors activator protein 1 (AP-1) and NF-κB [33–36]. Of note, whether this pathway is relevant or not to physiological angiogenesis requires further investigation [37]. Additional reported biological effects of extracellular acidification include immunomodulation [38], modulation of bone homeostasis [39], and contraction of airway smooth muscle cells [40].

Importantly, lactate and H^+ exert some of their biological effects independently of each other, though sometimes through redundant pathways leading to a same biological effect, as for angiogenesis. In other cases, they can have antagonist effects: lactate was shown to stimulate extracellular matrix synthesis by chondrocytes, whereas extracellular acidification inhibited extracellular matrix synthesis and chondrocyte proliferation [41]. As a polymer controlling the release of lactate and H^+, PLGA could thus be considered as an active ingredient when lactate and H^+ exert a biological effect that can influence the evolution of a specific disease.

3. Pharmacological effects of PLGA *via* sustained source of exogenous lactate *in vivo*

In 2003, Trabold et al. used for the first time a PLGA mesh as a lactate-releasing polymer on purpose in the fluid of a wound cylinder implanted in rats [42]. PLGA was shown to significantly elevate lactate level of 2–3 mM at steady-state in the wound fluid whereas higher levels of VEGF and collagen deposition were concomitantly observed in the cylinder. Based on this work and on the hypothesis that the application of exogenous lactate would accelerate angiogenesis and wound healing processes, Porporato et al. reported a pre-clinical study using a PLGA implant to supply lactate sustainably. *In situ* microdialysis revealed a local 3-fold elevation of lactate concentration as compared to