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Self-assembled multi-ring formations of glutamine and a possible link to erythema gyratum repens

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ABSTRACT

In the body L-glutamine is abundant and required for the proliferation of cells. Indeed human physiology is dependent upon having and maintaining the correct glutamine levels for a range of functions including neurological signalling and a healthy immune system. However, during tumourigenesis cell proliferation demands elevated levels of glutamine, which can ultimately lead to muscle atrophy. In some cases the skin provides the first indications of the underlying disease and erupts in a wave of complicated pattern formations. One such skin marker is erythema gyratum repens. We investigated the pattern formations associated with concentrations of glutamine in aqueous solutions at levels higher than that of a normal biological functionality. We find remarkable similarities between the patterns of erythema gyratum repens and the unusual self-assembled patterns of glutamine. The findings may lead to new therapeutics and understanding for those working in oncology and toxicology. Utilising the formations associated with glutamine could also assist in bio-functionalising micro and nanoparticles for high efficacy.

Introduction

There are many cases of diseases or symptoms arising as a precursor or marker of a more serious ailment [1]. For example, a paraneoplastic syndrome such as erythema gyratum repens (EGR) sometimes emerges as a result of the presence of a cancer in the body, even though it is not due to an immediate local presence of a cancer to the skin. The patterns on the skin can be remarkable including concentric rings and fractal-like geometries. They emerge as a result of a change in body chemistry due to excretions by the tumour cells or an immune response. The healthy structure of the skin can also become disorganised with illness [2]. In the case of EGR the whole body can become covered, with an advance of about 1 cm/day, that persists with advancing serpiginous trails [3,4] and nonspecific histopathologic features [4]. Here we hypothesise a link between L-glutamine and EGR, for those with access to facilities to carry out mass spectrometric analyses of biopsied specimens from each ring and normal skin between rings from EGR. This should be done for quantitative determination of L-glutamine. It should be noted throughout that the size of the effect is scalable with the volume of liquid across a surface but is explored under the microscope for sample sizes up to several centimetres.

We find that the polycyclic rash has all the hall-marks associated with elevated levels of L-glutamine (gln). As the most abundant free amino acid found in the body [5] it has an important functionality for the healthy growth of normal and neoplastic cells. But cancer is also glutamine hungry and so thrives on the transport of the amino acid into tumour mitochondria [6]. The continual perfusion of 0.5 mmol of glutamine creates a steady state condition whereby one glutamate is released for each glutamine absorbed [6,7]. Thus the cancer acts as a factory that depletes the levels of glutamine in the body. The reach of malignant proliferation peaks just after the tumour amidohydrolase enzyme glutaminase maximum in expression and activity (giving the reaction, $gln + H_2O \rightarrow glutamate(glu) \pm NH_3$) [6]. Thus, the first physical signs of tumour harvesting of gln could be the reaction of the skin, such as in EGR, which is a situation corroborated by actual cases [8].

Deprivation of glutamine can retard the growth of a cancer [9] but it is a complicated metabolism with both glucose and glutamine required as the major ingredients for proliferating cells, generating ATP and carbon for the synthesis of macromolecules [10]. However, it is detrimental to the sufferer of cancer to reduce intake of glutamine because the cancer begins to relinquish the body of its stores, leading to muscle deterioration [11]. The glutamate converted from gln will result in either nitrogen released through NH_3 or given up to amide nitrogen biosynthetic routes. For successful proliferation of cells the biosynthetic activity has to be directed at recreating macromolecular biostructures and this need is met by an anabolic shuffle of cellular metabolic action [12]. Thus it is clear that there is a pronounced glutamine activity

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associated with cancer and that even with low amounts of glucose present for energy sustenance, the cancerous cells can survive on glutamine very effectively. Therewith, we begin our discussion of the connection to the skin, the nucleation of glutamine crystallisation and skin markers such as EGR.

Results

Epidermal barrier function and glutamine

Localisation of glutamate in the epidermis may lead to signatures of pre-eminent biological discord in some individuals. In the event of low glucose supplies a cancer adapts itself to glutamine harvesting in order to maintain its development and growth. Signatures of cancer may show in the event of mild skin barrier damage or an allergic response of some form. Indeed skin barrier disruption has been shown to cause the secretion of glutamate shortly afterwards from the skin tissue [13]. The metabolic systems in the epidermis could be regulated by glutamate receptors. The skin cells for regulating and implementing an immune response are macrophages, Langerhanse cells, monocytes and mast cells. From the perspective of earlier prediction of cancer it was recently shown that for pancreatic ductal adenocarcinoma that there occurs an increase in branched chain amino acids even two to five years before diagnosis [14]. This is further evidence that biomarkers of cancer are to be found as alterations to the metabolic state, with protein breaking down throughout the body to feed the process.

We are interested in the development of the ring-like structures that emerge several weeks before the diagnosis of, for example, lung cancer on the skin in some patients. We will show in the next sections that these rings are a characteristic of high levels of gln. The shear abundance of gln in the body, higher than all other essential amino acids combined [15], is important for ensuring cell viability. The cutaneous manifestations often mirror the health of the visceral sites and metabolic effects due to tumour cells. EGR is not the only early skin warning of a tumour, though it is known to be the most strongly linked to an impending detection. Urticaria also commonly appears, but can be associated with a range of allergic reactions and so is not a definitive indicator of tumourigenesis [16].

In any case pattern signatures on the skin allow identification of many underlying problems by those working in dermatology and also in understanding cutaneous diseases at a microscopic level. In EGR the patterns also appear to be marked by collision fronts and a highly dynamic evolution with little by way of explanation in the literature about its basis. Gilmore gives a chemical pre-patterning hypothesis with a chemical gradient as a wave that spreads out across the skin, calling upon dynamical symmetry breaking concepts by way of explanation [17,18]. However, description of the chemical pathways has not been elucidated and the mechanisms of the condition remain unknown. Here, we hypothesise that the mechanism is associated with a wave of cutaneous gln reaction, based upon our experimental observations.

Glutamine transport

Glutamine is composed of two side chains containing nitrogen, one amide and an amino group, making it chemically suitable for free flowing transport of nitrogen throughout the blood. Thus, it ships ammonia through the peripheral tissues to be processed by viscera, such as the liver, for removal [19]. The abnormal growth of cells can eventually lead to neoplasia and for this to occur the blood has to be rich in gln. Thus, the transport of glutamine throughout the body becomes accelerated with metaplasia occurring.

In the development of lung cancer an irritant such as cigarette smoke, polycyclic aromatic hydrocarbons [20,21] or even radon gas [22] can eventually lead to the formation of metaplastic regions that result in dysplasia and then neoplasia. Cancer cells rely on glutamine to keep the tricarboxylic acid (TCA) cycle going [23]. Aberrant cell proliferation occurs with the activation of oncogenes such as pten and c-Myc, the switching off of the p53 tumour suppressor, and the redirection of glutamine via the mTOR-signalling pathway [24]. Understanding the altered metabolism of cancer and the development of an effective coupling between organs with the movement of glutamine throughout the body may be of benefit to create a decrease in resistance to apoptosis. Ko et al. have shown very clearly that gln affects cells differentially in the micro-environment of the tumour, with decreased autophagy for the epithelial cells and the opposite in the stromal compartment [25] – gln uptake and release seems to be energetically efficient in cancer cell proliferation, which in turn can lead to new mechanical stresses on the micro-environment [26,27].

Thus, whereby the tumour may once have been perceived as inefficient, it may be that new insights into the mechanisms of glutamine transport and regulation are showing that there is more purpose behind the drive for proliferation. One may even view the tumour as a kind of glutamine pump with the whole body becoming involved to some extent. The wave of glutamine would appear to be tidal as Gilmore stated [17,18].

We now wish to present the crystallisation phenomena of gln, which we have found are markedly different from those of other amino acids. Glutamine will move across a substrate as a wave as is shown in Fig. 1. In the intracellular fluid, especially of skeletal muscle, the concentration of gln ranges between 10 and 30 mM under normal conditions [28,29]. In circulation it is between 0.5 and 0.8 mM [28,29]. We are interested in abnormally high levels of glutamine with respect to biological functionality, so we demonstrate high concentration levels in aqueous solution (>20 mM). Fig. 1 is used to illustrate the remarkable wave like characteristics that occur in glutamine across a substrate. In Fig. 1(a) and (b) the optical microscopy images show the formation of ripples and domain boundaries that become evident as the evaporation occurs, in a dynamic process that can be analogous to morphological changes that emerge during dehydration of amino acid rich bio-liquids close to the skin surface. The next two images of Fig. 1 show large crystal structures that typically form close to interfaces between materials or at points where there are surface defects. Fig. 1(d) shows crystallisation in a blood sample at elevated concentrations. The process brings to mind the "Litos" test-system that tries to discern underlying diseases through the drying of biological samples and the resulting self-organised structures that are used to understand the metabolic state of organs [30].

Except that in the case of the skin the signatures are in clear evidence through, for example, EGR. For levels of gln similar to that found in the skeletal muscle, large crystal structures form around the perimeter of a droplet or interfacial boundary with some areas of clustered semi-circular concentric ringing. Fig. 2(a)–(d) show this for a concentration of 20 ± 5 mM, where all pattern formation has occurred at the edge, with a central region devoid of any wave-like spreading or crystal nucleation. The edge of the droplet is reasonably pinned to its original location throughout, giving a constant contact-diameter where the larger crystals will tend to form at all higher concentrations.

When the concentration is increased to 40 ± 5 mM, Fig. 3, the effects remain bound to the perimeter, though the size of the crystals do become larger. Small "buds" such as in Fig. 3(c) can emerge and as the concentration increases these will act to direct the internal structural formations. These kinds of larger crystals always nucleate first and can control the direction and onset of domain structures (see e.g. Fig. 1(a)). With regards to crystallisation, there

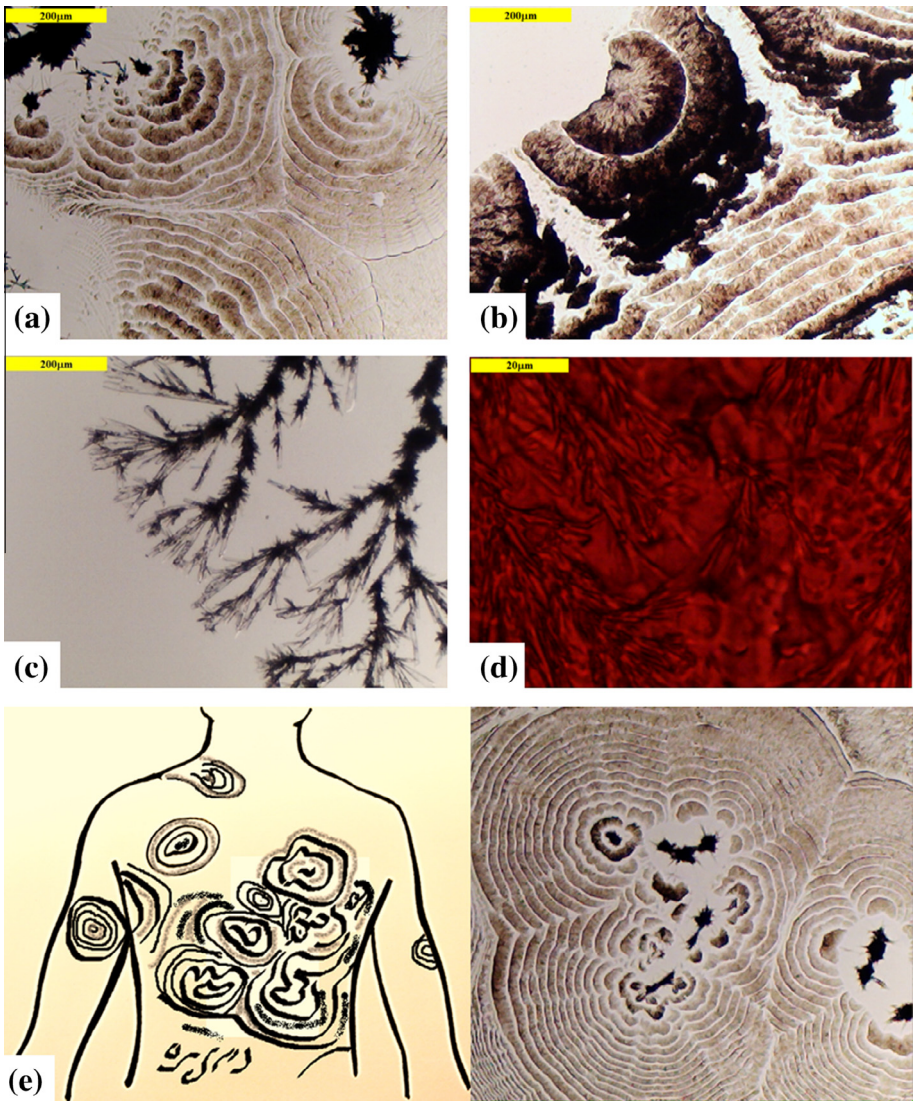

Fig. 1. L-Glutamine crystallises as a wave through water. In (a) the formation of domains marked by collision fronts and the appearance of ring structures is apparent. (b) The rings appear at junctures of the wavefronts, with larger crystals appearing at the periphery of a droplet or around a defect, as in (c). (d) Glutamine crystals developing in blood. (e) Similar patterns emerge in erythema gyratum repens (left sketch) and the polycyclic rash is compared to the self-assembled glutamine structures (right).

are precedents to finding related skin ailments biologically. For example, gout is a condition associated with concentrations of uric acid in plasma that exceeds its solubility, forming monosodium urate crystals (tophi) that lie under the skin. Thus, an increase in concentration, perhaps through build up over time as in gout, leads to larger crystal formation and for skin ailments greater inflammation. There has also been documented evidence of an association of the appearance of EGR to rheumatoid arthritis [31]. Fig. 4 shows that increasing the concentration of gln so that there is 65 ± 5 mM leads to enhancement of the peripheral crystal structures, whereas again a tidal like pattern moves inward from these outer edges till a point where it stops in the interior of the stain. We find that at a concentration of 90 ± 5 mM that the wave covers the entire interior space with an absence of surface vacancies on the higher scale. In the interior of a drop or between pinning sites concentric rings appear with regularity at this concentration, as shown in Fig. 5. These kinds of rings remind one of the incredible patterns associated with some cases of EGR. These concentric structures, with the appearance like beetroot rings, completely self-organise within the regions relatively far away from the large exterior crystals; such as those of the top picture in Fig. 4. To create rings such as these many methods have been employed in industry, ranging from use of low frequency vibration to manipulation with electromagnetic fields of fine particles. However, here the rings form under a simple chemical energy pathway without complex intervention. Thus, though the aim is to understand better the mechanisms of skin conditions from elevated gln levels it is also worth keeping in mind that there can be technological uses for this kind of self-assembly and the diversity of amino acids [32]. Not least of which is the creation of new optical devices such as super-oscillatory lenses produced from concentric rings of micrometre periodicity [33] or the surface layering of nanoparticles [34,35]. However, for biological issues the appearance of rings is particularly interesting as a function of concentration because of EGR and other skin anomalies. In the Supplementary information even higher concentrations of gln are investigated whereby rectangular crystals appear.

Discussion

We have demonstrated the formation of self-organised patterns that are associated with glutamine and its derivatives as a possible

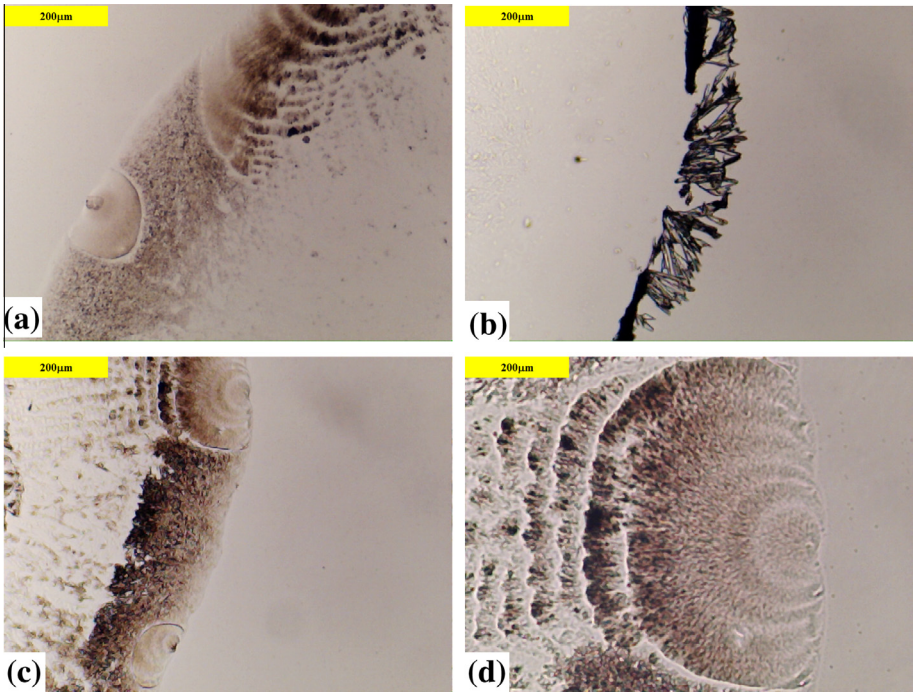

Fig. 2. Concentric ring structures emerge at concentrations of 20 ± 5 mM of glutamine in water in the boundary of a droplet. (a)–(d) Show these structures at different locations around the periphery.

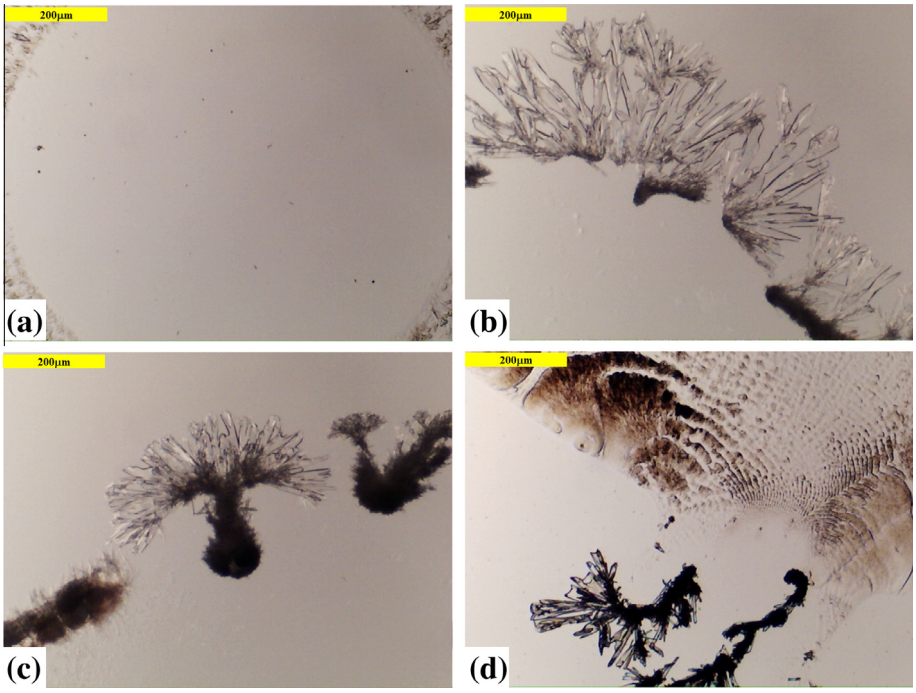

Fig. 3. L-Glutamine at 40 ± 5 mM in water. (a) As in Fig. 2 the central region is devoid of crystallisation and only an outer perimeter exists. (b) The crystals become larger at the outermost region compared to lower concentrations. These crystals can form as "buds" as in (c), whilst there are some more ring like structures at locations around the edge, (d).

link to EGR given strong evidence of elevated gln levels in the body as a consequence of tumour activity [6]. There are a few viewpoints to the origin of EGR, including cross-react antibody theory [4]. The purpose of this paper is to suggest glutamine as the reason for the unusual skin patterns and to prompt those with medical facilities to carry out a more direct experimental set-up using the actual skin or cutaneous cells to investigate the issue, for which the key molecules that forms ring structures in EGR remain unknown.

The physiological mechanisms underlying the development of skin rashes are highly complex. Interestingly, lamotrigine (a drug associated with the treatment of epilepsy), also with H_2N and NH_2 side groups is associated with skin rashes [36]. Taking a broader picture, as well as epilepsy, neurological diseases [37] such

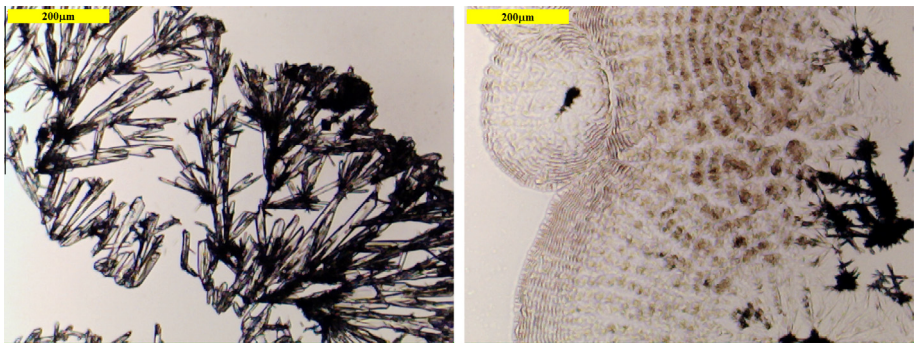

Fig. 4. Around the edge large crystals form (left). A wave-like formation is generated that moves inwards from the peripheral larger crystals (right). Always the edge crystals become visible first. The concentration of gln in aqueous solution was 65 ± 5 mM.

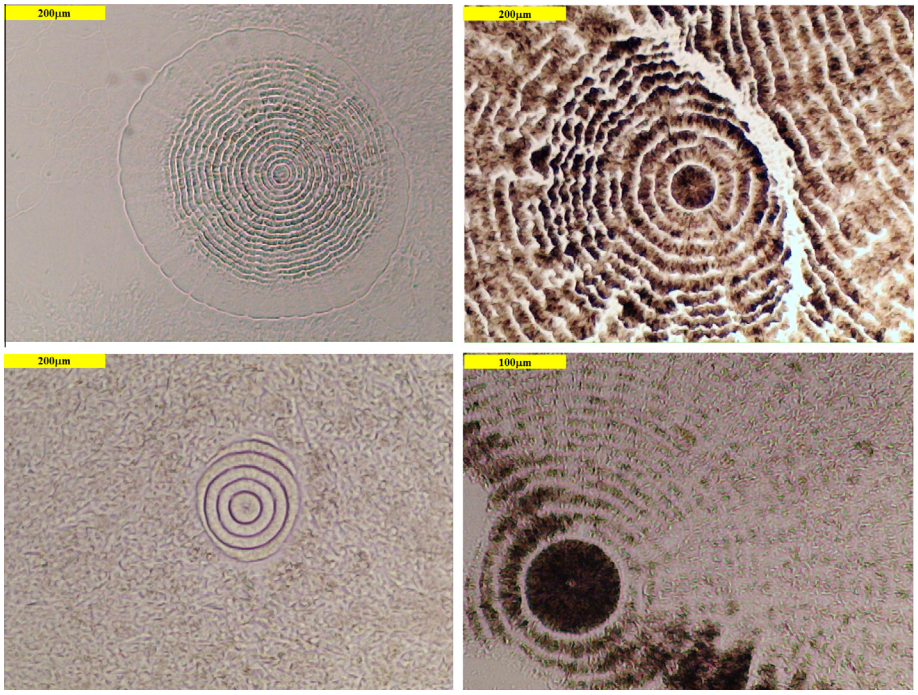

Fig. 5. With a concentration of gln in H2O of 90 ± 5 mM concentric ring structures appear in the bulk regions of the droplets and between confinement regions.

as Alzheimer's, and also strokes and head trauma lead to the release of high levels of glutamate in the brain. The role of glutamate has been extensively investigated by Teichberg and co-workers with respect to its role as an excitatory neurotransmitter [38,39]. In particular, it was discovered that glutamate is involved in almost every role of healthy brain function and central nervous system development. However, in some cases stroke may produce a glutamate cascade that can cause irreversible damage to the brain [40]. The increase in concentration of glu leads to the excitotoxicity [39], again demonstrating the importance throughout the body for regulation of these amino acid levels.

We know that there is a link between lung cancer and EGR and we assert to the concept that glutamine metabolism is at the root. Indeed it has been shown that glu may leak from the skin if it is injured, leading to a higher occurrence of skin inflammation, with Norkland et al. hypothesising that under stress the skin may compensate to maintain sufficient levels of amino acids [41]. It has also been known for a number of years that glu is not only a neurotransmitter but also functions in signalling in non-neuronal tissues, including keratinocytes in skin [42]. Importantly, keratinocytes manufacture and release L-glutamate [43] continuously and uniformly throughout the epidermis. Thus, upon saturation of the body with a glutamine related sequence of chemical reactions, brought about by the hunger of a tumour, the appearance of skin rashes seems highly plausible given the evidence of a delicately balanced state for healthy functionality. Also, to compound the problem, dermatitis lesions have also been linked to production and liberation of excess glu [44]. Thus, the glutaminolytic pathways are essential for understanding cancer biology [29] and consequently the complexity of the interactions occurring across microscopic and macroscopic scales.

We have shown the relationship between advancing serpiginous trails, with notable ring formations emerging as a function of concentration in aqueous solution. It is now important to investigate further the relationships of the glutaminolysis, cancer cells and the skin. For future work a clarification of how chemicals penetrate, accumulate and rise from beneath into the epidermis sub/intra/extra-cellular compartments needs to be undertaken, with a focus on amino acid units. This work may be undertaken using specialised two-photon microscopy which allows the detection of specific cells, proteins and amino acids near the stratum corneum whilst tracking substances as they are absorbed.

Interestingly, glutamine has been investigated and found to enable the coupling of exergonic (negative Gibbs free energy change: flow of energy from the system to the surroundings) and endergonic processes (non-spontaneous absorbtion of work from the environment to the system) that may not happen together or be localised in the same tissue [45]. Thus, the view of glutamine as a systemic-wide enabler of energy transfer is valid. We hope that the work herein can offer valuable new insights into the role of gln in skin signatures (e.g. EGR) of interior diseases such as lung cancer.

It is also important for the development of new drugs or technologies that are designed for exploiting signal transduction theory [27,46,47] to better understand the transport of glutamine inside the body and how it can lead to adverse bio-responses when the concentration becomes too high or low because it may be a tool against cancer. In the biofunctionalisation of nanoparticles that target cancer, surface coatings are essential to maximise their efficacy and to even reduce their cytotoxicity in some cases [48]. Being biocompatible also allows the clearance of nanoparticles from the body in a natural way [49] and so surface preparation is crucial. There is a high activity of crystallisation at the periphery of droplets containing glutamine that can dictate the assembly of the interior patterns that we have seen which may be used to coat a surface. This is also true around an artificially induced defect or a "pinning" site (glutamine is particularly suited for creating artificial structures, an example of which is in Fig. S8 of the Supplementary information, whereby a micro-square lattice was prepared). Cytotoxicity also occurs with a dependency upon the size of the crystals formed and thus concentration [50]. A different perspective for the presented results is that the pattern formations elucidated upon may be useful for the preparation of the outer layers of micro and nanoparticles as a function of concentration which could be beneficial for creating pharmaceutical nanocarriers [51] enveloped in glutamine.

Methods

Different concentrations of gln were prepared by addition to bi-distilled water at room temperature and then sonicated for 6 min at 46 kHz after centrifugation for 10 min at 1000 rpm. The solution was then dropped, using micro-syringes, onto a clean soda-lime glass slide, with a liquid–air interface. The air interface is deemed valid for making comparisons to skin effects and the experiments were conducted when the temperature of the slide reached 35 °C (measured with an infrared thermometer). The self-assembly was monitored using optical microscopy (OM) and a digital camera was attached to the lens. The surface of the substrate was scanned manually for the concentration dependent formation of the rings using OM.

Competing financial interests

The author declares no competing financial interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mehy.2015.03.012.

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