Old King Coal — molecular mechanisms underlying an ancient treatment for atopic eczema

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Traditional remedies for common disorders have been known for centuries, but insight into their mechanism of action is often limited. In this issue of the JCI, Joost Schalkwijk’s research group at the Radboud University Nijmegen Medical Centre in The Netherlands advances our understanding of why topical coal tar is an effective treatment for atopic dermatitis (AD), both rationalizing the use of this traditional medicine, and providing the scientific basis for new therapeutic approaches.

AD (also called “eczema”) is the most common inflammatory skin condition, affecting about 20% of children in the developed world. AD is a classic complex trait where a combination of several genetic predisposing factors interact with environmental stimuli to trigger the disease. AD is frequently associated with high serum IgE and a Th2 immune response (1, 2). In 2006, a paradigm shift in the pathomechanistic understanding of AD took place when loss-of-function mutations were discovered in the FLG gene encoding the skin barrier protein filaggrin in the common monogenic skin disease ichthyosis vulgaris (dry, flaky skin) (3). Soon thereafter, these same filaggrin variants, which are carried by about 10% of populations of European ancestry and persist at high frequencies in other populations (4), were shown to be the major genetic predisposing factor in AD (5). Filaggrin-deficient animals were subsequently shown to have a “leaky” skin barrier, allowing passive percutaneous transfer of antigens, which trigger skin inflammation and an allergic immune response, analogous to AD in humans (6). This work showed that a primary skin barrier deficiency is at least one important factor in AD pathogenesis, although Th2 immunity is clearly also a major player (1).

Making the pitch for pitch

Coal tar has been used medically since ancient times. In his epic 5-volume work, Ἐλευθερίας τετρακάθες (Latin: De Materia Medica), the Greek physician, pharmacologist, and botanist Pedanios Dioscorides (circa 40–90 CE) chronicled many and varied herbal and other remedies in use at the time, including the “grime of a gymnium wall.” While this remedy for abrasions and ulcers does not currently enjoy popularity, his suggestion of the use of bitumen or asphalt/coal tar for “inflammation” (7) has maintained traction over the succeeding 2 millennia (8). For as long as modern dermatology departments have existed, liquor picis carbonis (LPC) has been a part of their working vocabulary, and preparations containing LPC are widely considered to be effective in the treatment of psoriasis and AD. Indeed, a recent systematic review provided evidence of the efficacy of 0.5%–5% LPC preparations for both these conditions (9).

Tar, asphalt, bitumen, and pitch are related substances consisting of complex mixtures of high molecular weight organic compounds that can be derived from heat distillation of plants, wood, petrochemicals, or coal. Pitch essentially functions as a solid but is really an incredibly viscous liquid that is estimated to have more than 100 billion times the viscosity of water (10). The world’s longest continuously running laboratory experiment is The University of Queensland’s “Pitch Drop Experiment” (10). Begun in 1927–1930 by Thomas Parnell (it took 3 years just for the pitch to settle into a glass funnel), droplets of pitch fall under gravity only about once a decade, with the next one expected this year. We live in exciting times!

A target identified

Although the terms are somewhat ambiguous and interchangeable, pitch tends to refer to the more solid substances in this group, and tar generally refers to the more liquefied products. Coal tar is an extremely viscous liquid obtained from dry-heating coal to temperatures in the range of 900°C to 1200°C, and is thought to consist of at least 10,000 distinct high molecular weight hydrocarbon and aromatic compounds,
A complex mixture will target AHR and few, if any, are likely to have the desirable drug-like chemical properties upon which to build a drug discovery program. Alternatively, high-throughput screening of chemical compound libraries could be used to identify pharmacologically tractable small molecules that act through the AHR and other downstream pathways.

While the effects of a complex organic compound mixture such as coal tar are likely to be pleiotropic, these new insights identify the AHR as a key regulatory pathway and therefore a potential drug target for AD. Although the differential effects of dioxin versus coal tar exposure on the AHR will likely need to be resolved by further experimental work in order to convince regulatory authorities to reassess the viability and safety of potential drugs that act on this pathway, the work of van den Bogaard et al. nevertheless sets the scene for an exciting new rational drug design program in this important common disease.

Clean coal?
It has recently been shown that coal tar applied to the skin is absorbed at low levels and excreted in the urine, making both systemic immunomodulatory effects and systemic carcinogenic effects possible (15). Given that AD most often initially presents in children less than 2 years of age, when transcutaneous absorption is enhanced and drug metabolic pathways may be immature and less effective, a proven safety profile would be very desirable. To this end, identification and purification of the beneficial pharmacologically active moieties in coal tar from those that are potentially carcinogenic would be of great interest for future drug development. There are two obvious approaches to refine coal tar therapy based on the data presented here by the Schalkwijk group. Chromatographic fractionation of coal tar could be employed to identify the key active components therein that activate the AHR, however, it is likely that a large percentage of the PAHs within this complex mixture will target AHR and few, if any, are likely to have the desirable chemical properties upon which to build a drug discovery program. Alternatively, high-throughput screening of chemical compound libraries could be used to identify pharmacologically tractable small molecules that act through the AHR and other downstream pathways.
commentaries

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Nucleocytoplasmic connections and deafness

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9. Slutsky JB, Clark RA, Remedios AA, Klein PA. The linker of nucleoskeleton and cytoskeleton (LINC) complex connects the structural networks of these subcellular compartments (Figure 1). The SUN-KASH binding within the perinuclear space retains the nesprin, which further covalently linking them (6). Suns are integral proteins of the inner nuclear membrane that also bind to A-type lamins of the nuclear lamina, a meshwork of intermediate filament proteins providing structural support to the nucleus. The SUN-KASH binding within the perinuclear space retains the nesprin, which also contains a transmembrane segment, in the outer nuclear membrane. At the other end of this transmembrane membrane bridge, different nesprins interact with unique cytoskeletal components. For example, nesprin-1 and nesprin-2 isoforms bind directly to actin, nesprin-3 via plectin to cytoplasmic intermediate

The linker of nucleoskeleton and cytoskeleton (LINC) complex connects the nuclear lamina to the cytoskeleton, in part to aid in nuclear positioning. Mutations in genes encoding LINC complex and lamina components cause a range of human diseases. In this issue of the JCI, Horn et al. report that mutations in the gene SYNE4 encoding the LINC complex protein nesprin-4 lead to progressive high-frequency hearing loss. Further, in mice deficient in nesprin-4 and Sun1, another LINC complex component, outer hair cells of the cochlea form normally during development, but die in the early postnatal weeks. These results link improper nuclear positioning specifically to the death of outer hair cells in the organ of Corti and ultimately to deafness.

The nuclear envelope is composed of the nuclear membranes (inner and outer), nuclear pore complexes, and nuclear lamina. It separates the nucleoplasm from the cytoplasm of eukaryotic cells, and the transport of proteins, nucleic acids, and other molecules among these compartments in interphase is restricted to the pore complexes. The nuclear envelope has been a growing focus of clinical investigation, as in the past 15 years a wide range of inherited diseases have been linked to mutations in genes encoding proteins of this subcellular structure (1, 2).

Nucleolar envelope and nucleocytoplasmic connections

Recent research has shown that the nuclear envelope not only separates the nucleus from the cytoplasm, but also connects the structural networks of these subcellular compartments (Figure 1). The linker of nucleoskeleton and cytoskeleton (LINC) complex mediates this connection (3). The core of the LINC complex forms from the interaction of SUN (Sad1, UNC-84) domain proteins with KASH (Klarsicht, ANC-1, Syne homol-