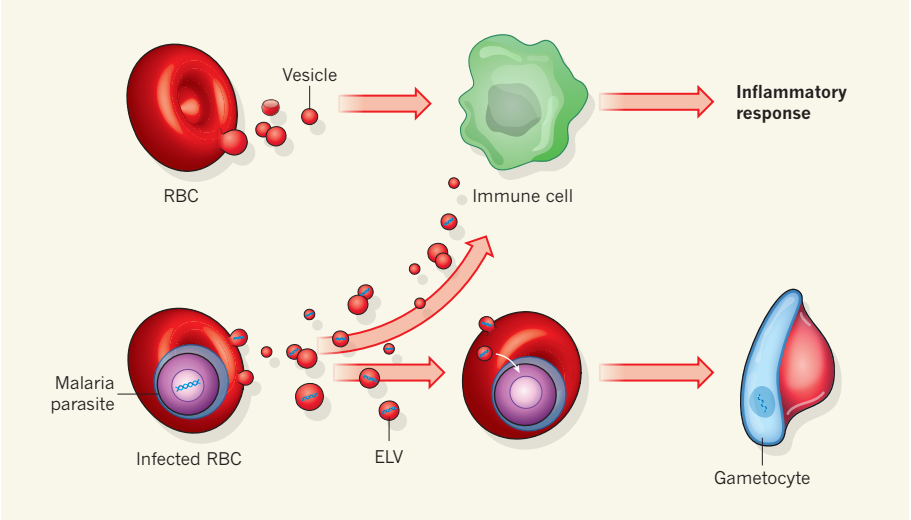

Figure 1 | Release of vesicles from red blood cells. Uninfected red blood cells (RBCs) shed cell-membrane-derived vesicles containing damaged cellular components. The vesicles are taken up by immune cells that digest and dispose of this cellular debris. Regev-Rudzki *et al.*[2] and Mantel *et al.*[3] show that RBCs infected with malaria parasites shed more vesicles, and that these exome-like vesicles (ELVs) can mediate transfer of parasite-derived DNA and proteins to other infected RBCs. This provides a form of parasite-to-parasite communication that, among other possible functions, can induce parasites in the recipient cells to differentiate from an asexual to a sexual (gametocyte) form. Vesicle release also contributes to the symptoms of malaria infections by activating inflammatory responses from cells such as macrophages.

mechanism for how asexual-stage parasites generate extracellular signals. Using complementary approaches, the studies demonstrate that small vesicles released from the cell membrane of cultured *P. falciparum*-infected RBCs can mediate the transfer of DNA (specifically, plasmids that encode drug-resistance mediators or fluorescent proteins) from one infected RBC to another. These extracellular vesicles range from 70 to 250 nanometres in diameter[2,3] and contain both RBC and parasite-derived proteins[3]. The authors refer to them as exosome-like vesicles (ELVs)[2] — by analogy to small vesicles that are generated in the endolysosome system of mammalian cells and shed extracellularly — or RBC-derived microvesicles[3]. The term ELVs will be used here.

Circulating microparticles originating from RBCs have previously been reported in patients with malaria[6] and in mice infected with the rodent malaria parasite *Plasmodium berghei*[7]; in the latter, these have been shown to have strong pro-inflammatory activity. Similarly, the ELVs characterized in the current studies seem to be involved in the inflammatory response. They are taken up by other host cells, including macrophages and neutrophils, leading to cell activation and the production of cell-signalling molecules called cytokines (Fig. 1). This may benefit the parasite by increasing the expression of receptors on the endothelial cells to which infected RBCs adhere, thus avoiding parasite clearance in the host's spleen[8]. It may also lead to deregulated inflammation and severe complications, such as cerebral malaria[9].

Remarkably, both groups found that ELVs are also internalized by other infected RBCs, leading to differentiation of parasites in the recipient cells into gametocytes (Fig. 1). The accumulation of ELVs in the serum of infected individuals may therefore constitute a signal that initiates and regulates the formation of transmissive parasite stages to maximize their passage to the mosquito vector. ELV formation seems to be enhanced by drug treatment[2], and so this process might also constitute a danger signal that drives the parasite into a resistant state.

The current data provide convincing evidence for parasite-to-parasite communication in *in vitro* cultures, but whether ELVs mediate communication at the low parasite densities that occur *in vivo* remains to be determined. An intriguing possibility is that ELV-mediated sequestration of *P. falciparum*-infected RBCs onto the walls of blood vessels could lead to a local increase in parasite density and aid vesicle-mediated communication.

Although the mechanism by which ELVs are formed is not known, it is well established that uninfected RBCs normally shed membrane vesicles, albeit at a much lower level than *P. falciparum*-infected RBCs. Vesicle shedding in uninfected RBCs is thought to be a mechanism for removing damaged proteins or membrane components[6,10] (Fig. 1). It is tempting to speculate that the malaria parasite has exploited this process to enable cell-to-cell communication. Genetic studies performed by Regev-Rudzki *et al.* suggest that ELV formation depends on the parasite protein PfPTP2, which is associated with vesicles in the RBC

50 Years Ago

Investigations were conducted here to determine the effect of a magnetic field on the ripening of green tomatoes (*Lycopersicon esculentum* Mill. Var. V. R. Moscow). Four permanent magnets of considerable strength were utilized. Fruits of uniform maturity were placed between the magnetic poles … The ripening rates of treated fruits were compared with those of untreated controls in the same room under similar conditions … In all cases the treated fruits ripened faster than the controls. Furthermore, the fruits nearest the magnetic south ripened faster than those nearest the magnetic north.

From *Nature* 6 July 1963

100 Years Ago

In recent issues of *Nature* several correspondents, in referring to the fact that a metal bedstead or a few wires stretched a few feet above the ground will make a wireless antenna, have overlooked a most important point, viz. that with such an antenna the ordinary methods of tuning are quite useless. A piece of wire netting suspended a few feet above the ground makes a most effective aerial, and enables one to receive loud signals from long-distance stations, but signals from Eiffel Tower, Cleethorpes, &c. will all be mixed up, and the ordinary tuner will not separate them effectively … Wireless signals that are feeble when the surface of the earth is dry, becoming stronger after rain, and the well-known fact that these waves travel much better over sea than over land, all seem to indicate that the aerial waves are *at least* supplemented by waves that travel along the surface of the earth.

From *Nature* 3 July 1913