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Highlights

The dual role of ROS, antioxidants and autophagy in cancer

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ABSTRACT

In this issue of the *Biomedical Journal*, we highlight a review revealing that the effect of autophagy, reactive oxygen species, and antioxidants in cancer may be a question of timing and context. We also discuss original research showing that the prevalence of cleft lip with or without palate in Taiwan has declined over the past 20 years, and what this might mean in terms of trends in abortion. Finally, we also learn about risk factors for recurrent hospital-acquired infection with multi-drug resistant bacteria, and the value of dental screening for patients with tinnitus.

Spotlight on reviews

The dual role of ROS, antioxidants and autophagy in cancer

Reactive oxygen species (ROS), including peroxides, superoxide and hydroxyl radicals, are a by-product of normal cell metabolism and important cell signaling molecules; yet, they are perhaps more infamously known for the role in ageing [1] and disease [2]. In excess, these molecules can cause irreversible damage to lipids, DNA and proteins. If ROS wreak havoc, cells can 'clean up' the mess they create through autophagy, in which damaged cellular components are degraded in lysosomes. Although these quality control pathways are generally thought to protect cells against the harmful effects of ROS, this view might not be so clear cut as explained by Hjelmeland and Zhang [3] in this issue of the *Biomedical Journal*.

The link between ROS and cancer initiation is a long-standing one. Besides the high levels of ROS in obvious environmental carcinogens such as cigarette smoke [4], ROS have been shown to be critical for the transformation of cells mediated by oncogenes or loss of tumor suppressors. For example, the downregulation of p53 leads to increased ROS levels and antioxidant-related drugs inhibit tumor formation in mice lacking this gene [5]. However, every tumor is unique, and the role of ROS and antioxidants can differ depending on the genetic, epigenetic, and microenvironmental variation present. Indeed, mouse embryonic fibroblasts expressing mutant G12V K-Ras have low levels of ROS [6], and in another model, high levels of antioxidant production through mechanisms such as the upregulation of Nrf2 offers a survival advantage [7]. Thus, the notion that

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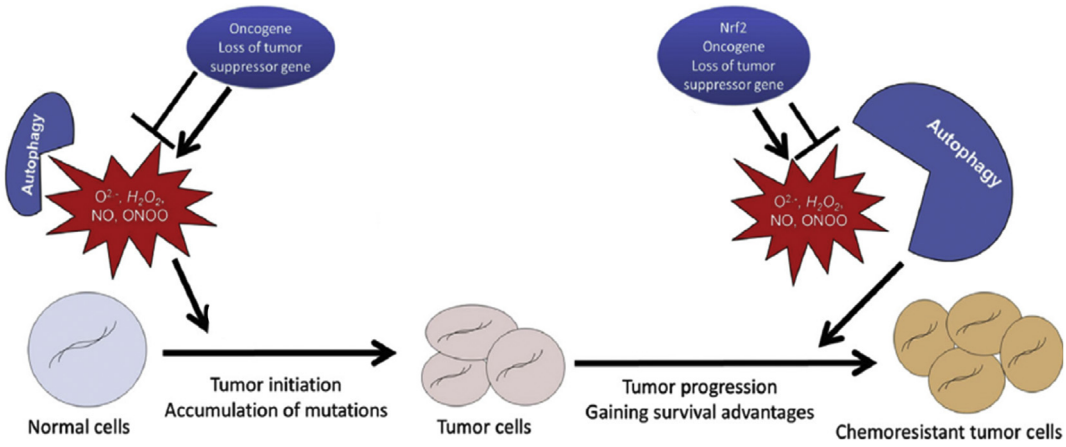

Fig. 1 – Autophagy and ROS in tumor initiation and progression. In normal cells, the accumulation of ROS promotes tumor initiation. Autophagy removes ROS-damaged cellular components, thus protecting against tumorigenesis. However, in established tumor cells, the removal of these components by autophagy offers certain survival advantages and may lead to chemoresistance. Figure adapted from Hjelmeland et al. [3].

ROS are 'bad' and antioxidants are 'good' depends to some extent on context.

This lack of a simple dichotomy also applies somewhat to autophagy. The accumulation of damaged proteins or organelles leads to the generation of autophagosomes, which encapsulate the faulty cell contents and deliver them to lysosomes for degradation. This process involves over 30 proteins and many cellular signaling pathways [8], the perturbation of which leads to tumorigenesis [9]. This makes sense because autophagy suppresses chronic tissue damage and maintains genomic stability, but again the relationship is complex. For example, depending on cell context, autophagy may promote tumor growth by suppressing the p53 response, sustaining metabolic homeostasis and survival in stress and preventing the diversion of tumors to benign oncocytomas [10]. In light of these findings, autophagy inhibitors such as chloroquine have been tested in cancer therapy [11].

Thus, the effect of redox status and autophagy in cancer appears to be a question of context, and in particular, timing [Fig. 1]. Although high levels of ROS and defects in autophagy promote cancer initiation, tumor cells with established genome mutations or rearrangements depend strongly on antioxidants and autophagy to gain survival advantages. How exactly to hit the tumor where it hurts will thus depend on complex phenotyping as part of the continuation of the quest to develop personalized treatments.

Spotlight on original articles

Drop in incidence of cleft lip/palate in Taiwan

Multiple factors have been linked to the development of cleft defects, including genetics, socio-economic status and in particular, environmental factors such as smoking, low folate consumption and drinking alcohol. While awareness about the dangers of smoking and drinking during pregnancy has increased over the years, so too has the use and accuracy of prenatal diagnosis by sonography [12]. In this issue of the *Biomedical Journal*, Chang et al. [13] report a drop in the incidence of cleft defects in Taiwan over the past 20 years, and suggest that this is due to an increase in the termination of fetuses with cleft defects.

Cleft lip and/or palate are the most common congenital craniofacial anomalies with an incidence of 1:700 to 1:1000 births depending on the population. These defects arise between the sixth and ninth week of pregnancy, when the tissues of the mouth and face are formed. Their treatment requires a multidisciplinary approach, involving surgery during the first sixth months of life, followed by subsequent surgical procedures and visits to a speech therapist, orthodontist, psychologist and specialist nurse.

Cleft lip was first diagnosed prenatally by sonography in 1981 [14]. Today, using 3D sonography, cleft lip with or without plate can be detected with an accuracy of 86–100% whereas a cleft palate alone remains difficult to diagnose before birth [15]. This improvement in technology has created a situation in which it is now possible in many countries to diagnose a cleft lip and terminate a pregnancy during the second trimester, all within the realm of the law. In Taiwan, abortion is legally permitted before 24 weeks of pregnancy if the fetus has severe congenital anomalies or causes detrimental effect to the mother. In 1995, following the establishment of National Health Insurance, prenatal sonography screening became readily available to Taiwanese women on a large scale for the first time.

To investigate the impact of widely available prenatal diagnosis, Jung et al. determined the rate of cleft defects in Taiwan between 1994 and 2013, during the introduction of National Health Insurance. They collected data from the two only Craniofacial centers in Taiwan where patients with clefts are referred. Out of nearly five million live births in Taiwan during the 20 year period, a total of 7282 new patients with