Novel function of keratin

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The greatest obstacle to knowledge is not ignorance, it is the illusion of knowledge.
–Daniel Boorstein.

Since the discovery of keratins, they were considered as molecular meshwork providing structural integrity and resilience to the epithelial cells. This unidirectional thought is challenged many times, and argued by a number of groups that they have modulatory roles in homeostasis of epithelial cells as documented by publications in the last decade[1–3]. However it has been enlightened by the group of P. A. Coulombe that keratin (K) has a regulatory role, indeed regulatory role in translation indirectly[4]. Regulation of such bulk translation, which is a vital process of cell, will have significant implications in wound healing and consecutively understanding the biology of keratins.

Keratin belongs to the family of intermediate filament proteins. They form heteropolymers and each member of the acidic family of keratin pairs with basic keratin proteins, in epithelial tissue specific manner. 2–8 keratins are expressed by all epithelia[5]. More than 60 different genes of keratin are identified from the human genome sequence; of them 53 are functional genes[6]. Thirty seven different polypeptides of keratin are isolated and named as type 1 and type II keratins because of their mobility on 2DE, the basic and the acidic keratin respectively. This information of abundance of keratin genes strengthens the idea of them having regulatory/modulatory function. Although there is redundancy in function of keratin proteins, there are still subtle differences in different keratins, which makes them mandatory for resistance of specific insults in a cell-type specific manner[7]. It is worth mentioning that oral cavity itself has different epithelium, namely epithelium of ventral tongue, dorsal tongue, buccal mucosa, alveolar mucosa, hard palate, soft palate, etc. and each of these epithelia expresses different set of keratins. This led us to think as to why we need tissue-specific expression of keratin. One reason may be for optimal tissue-specific function and to enable tissues to respond to stress better.

Complexity of keratin expression is illustrated by hair cells which express more than 20 keratins during their lifetime. Strikingly, absence of a single keratin (K 17) can alter the differentiation programme of cells leading to premature entry into catagen stage of hair cycling[8]. This exemplifies the importance of single keratin in preservation of homeostasis. For a long time keratin 8/18/19 have occupied the focus of researchers owing to its aberrant expression in many malignant stratified epithelial cells/other cell types. However K 17 has now been shown to have a regulatory role in translation and has been assigned a function which albeit many other keratins await. Investigation on its aberrant expression in psoriasis and carcinoma warrants further study.

While investigating the expression of keratins as a response to wound, Coulombe's group identified Kb6a, and Kb6b and K 17 are up-regulated in the neighbouring cells close to the wound. They observed that Kb6a and Kb6b double knockout embryos do not show delayed wound closure, however K 17-/- exhibit delayed wound closure. Further research revealed that cells around wound of K 17-/- embryo are smaller. Ruling out the possibility of altered cell cycling and cell-matrix attachment, led to the thought that there might be alteration in cell growth mechanisms. Investigation on mTOR pathway which regulates translation, led to the discovery of blunted activity of mTOR, in absence of K 17-/- as depicted by the substrates (p-4EBP1 and p-S6K) which mTOR phosphorylates. This decrease in mTOR activity resulted in decrease in bulk translation and in turn retardation in cell growth. Concomitantly, decreased level of phosphoAkt was elucidated indicating that keratin regulates translation via AKT-mTOR pathway. They also ruled out the possibility of involvement of other growth-associated signalling kinases like Erk 1/2, p38 MAP kinase and JNK.

In order to dissect the mechanism of this deregulation, scientists went ahead to find out the interactors of K 17 in cultured epithelial cells and found that 14-3-3σ interacts with K 17 in a probable phosphorylation-dependent manner. 14-3-3σ is found dispersed in normal cell; however in K 17-/- cells it was found predominantly in the nucleus. Ectopic K 17 expression in K 17-/- cells, led to an increase in translation and rescue of all the events, which were a result of K 17 knockout. Reorganization of 14-3-3σ proteins could occur and it can now localize to cytoplasm also. Hence it was demonstrated that keratin regulates translation in a 14-3-3σ-dependent association, as mutation of two residues, which are important for 14-3-3σ binding do not show increase in translation.

This exciting work on keratin function is probably the tip of the iceberg and hence certain key questions still need to be addressed. How keratin regulates mTOR/Akt pathway – whether the mechanism is direct or indirect – still needs to be discovered. Keratin 17 interacts with 14-3-3σ; however what links mTOR to this K 17 +14-3-3σ complex is its forming a trimeric complex or an adapter protein/signal protein link which relays the message to mTOR. It will be worth finding out the binding partners of K 17 and 14-3-3σ. Do all keratins regulate/modulate protein synthesis to a certain level? Does keratin phosphorylation in any way associated with signalling via desmosomes or hemidesmosome ultimately affect the cell proliferation/growth? What replaces keratin in non-epithelial cells like B cells, T cells? If intermediate filament like desmin and vimentin could replace keratin in certain other cell types, then why is only keratin 17 transcription induced in response to wound? Recent studies have indicated role of TGF β3 in wound healing and documents that serum causes migration of epidermal cells and that TGF β Receptor II is associated with keratinocyte migration[9]. Also other studies point towards the association of TGF β in keratin biology[10]. Investigating the transcriptional regulation of keratin 17 (because of distinct upregulation of K 17 where 16 more keratin genes are present in Type I cluster) in response to wound (via investigation of local cytokines and chemokines) will give insights into the role of these interesting proteins in homeostasis of epithelial cells.

As the research on keratin moves in quest for molecular mechanisms that keratins play with, understanding their significance is becoming more complex as keratin research asks more questions than answering some. Scientists are still to unravel the beautiful complexity of molecular mechanism regulated by different keratins, which will aid us to comprehend cell biology better than we do now.

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